

Cholera Prophylaxis is Plumbing and Prosperity

THE sad condition of Bengal will remain as a sombre reproach to developed nations for many years to come. That circumstances could have arisen in which several million people should feel it prudent to pack up their belongings and move to an unfamiliar place is an echo of the way in which migration was forced on mediaeval people by events over which they had no control. It is, of course, insufferable that similar migrations should be forced on all too innocent populations at times when individuals in developed nations are confident that, even if they do not own a second motor car or a colour television set, they are at least their own masters. Since the Second World War, there has been no marked decrease in the prevalence of refugees and in that spirit practical men will no doubt be concerned not so much with making the columns of refugees go away as with working out ways of accommodating them more easily. The occurrence of cholera, a threat ever since the army of Pakistan moved against the recessionists, is one of many symptoms to be treated.

By now, natural as well as artificial disasters are frequent enough and damaging enough for the threat of disease of some kind to be recurrent. Earthquakes in Turkey or the Andes constantly provoke fears of cholera epidemics and so too do natural catastrophes such as the typhoon that killed a million people in the Bay of Bengal less than a year ago. Most often, the threat turns out to be ill-founded. Disaster strikes but nothing follows. This no doubt is why the threat of cholera among the refugees in East Bengal seems to have lain dormant for the best part of a month. After all, the time for flying vaccine and saline solutions to Calcutta was the beginning of May, not the beginning of June. To be sure, it would be unreasonable to expect that private companies would make speculative arrangements of this kind—they have no particular reason to tie up resources in ways like that and indeed they might be considered ghouls for seeking, as it might seem, to turn disaster to their own advantage. So how are steps to be taken for avoiding sudden shortages of medical supplies like those which have become apparent in the past few days? Is this not a situation in which some international organization should act as a banker, keeping a lien on available stocks, wherever manufactured, against emergencies which might arise, and being prepared to release these to the ordinary commercial markets in other circumstances? This, in practice, is the way in which the orderly distribution of raw materials such as tin is administered. The advantage of such a system, and the goal to which both the manufacturers of vaccines and other medical supplies as well as the international aid-giving authorities should work, is the benefit that comes from making a diversity of supplies available to a common pool. And is it not necessary that arrange-

ments like these should be administered not by national governments but by the specialized agencies of the United Nations? Where cholera is concerned, the orders of magnitude are, after all, easy enough to predict. There is probably a continuing need for some millions of doses of vaccine and for enough saline solution to treat 100,000 patients or thereabouts. Keeping such a stockpile fresh ought not to be an insuperable task. Similar precautions should, of course, be taken to guard against the threat of diseases of other kinds, from plague to yellow fever.

As it happens, exactly similar arrangements are necessary if the United Nations is to be in a position to deal with other kinds of international disasters, from typhoons to earthquakes. The experience of the past few years has shown quite clearly that there is a need for an internationally accessible pool of helicopters and for ways of moving communications equipment into regions where existing arrangements are disrupted by emergencies. Here again, the United Nations or one of its agencies should be given a lien on facilities rather than outright ownership of them. The chances are that thoroughly commercial organizations would be prepared to come to an accommodation of some kind with the international agencies. The cost need not be excessive, but the unhappy lessons of the recent past argue for speedy attention to the problem.

In the long run, however, no amount of vaccination will be sufficient safeguard against cholera. The long-term defence must be better plumbing, not simple vaccination. It is also relevant that the incidence of cholera, like that of many other diseases of the developing countries, is closely dependent on nutrition. People who are well nourished are much less susceptible. It follows that the best defence against cholera is nothing less than the old-fashioned recipes which the aid-givers have been advocating for decades—the general improvement of health and welfare. It goes without saying, of course, that by comparison with the cost of the vaccines which have been rushed to Calcutta this week, this is enormously expensive. To provide a developing population of a million people with decent housing and plumbing would no doubt cost much more than the annual product of the nations to which they belong, but it would also require changes in the balance between city and rural life. In the long run, it is of course unthinkable that such facilities could be financed from sources other than the productivity of the people concerned, which in turn implies that the ultimate defence against cholera and diseases like it is not even plumbing but prosperity. It may be too much to hope that mere economic advancement will remove the underlying causes of the unhappy migration of the past few weeks but there is at least a chance that it could take the edge of some of the anxieties which the migration has caused.



Ready to Go but Nothing to Go In

IF precedence is any guide, the successful launching this week of another Russian spaceship with three pilots should help the faltering National Aeronautics and Space Administration in the United States to win a little more support for its plan to construct a shuttle rocket (see page 346). This time, however, neither Congress nor the Administration is likely to be influenced by considerations like those which, in the fifties and sixties, allowed the military agencies and their associates in the United States to bolster up their own plans with reports of how serious was the competition from abroad. For one thing, this is still a bad year for the United States economy. For another, this Administration has outdone even its Republican predecessors since the Second World War in prudence, some say parsimony. But, more important, the errors of NASA's ways in the past few years are taking their toll. By public confession, officials of NASA have in the past acknowledged that one of the functions of the plan to design and build a rocket vehicle able to carry objects into orbit and then to return was to provide a tangible technical goal at which the great resources of NASA could be aimed. To be sure, it is always easy to point to other advantages—if by the late seventies it would be economically feasible to launch scores of satellites a year, what would be more sensible than to carry them up in batches in a shuttle rocket and then, almost literally, to throw them over the side? None of the arguments in favour of the shuttle has, however, provided cause for thinking that the demand for Earth satellites in the late seventies and eighties would be great enough to justify the development. Indeed, from the beginning, the shuttle has had all the appearance of being a device that would create for its designers the need for credible employment. To Congress and to taxpayers in the United States, in other words, one of the first features of the shuttle project is not the cost of development but the cost of finding work for the finished product. This, no doubt, is one of the reasons why the attempt to interest European governments in collaboration has so far been a failure.

By all accounts (see page 347), however, NASA's attempt to win friends among scientists with a plan to send a rocket to the distant planets is also turning sour. It remains to be seen whether the Grand Tour will materialize and even though there is no doubt that such an exploit would return to Earth a useful yield of infor-

mation (see *Nature*, **231**, 145; 1971), it is even more certain that the money could be spent more usefully on more humdrum exploits. It remains a source of wonder to scientists outside the United States that the excitement in the past few years about the scientific value of space exploration has been accompanied by what seems to be a moratorium on the construction of radio telescopes. Plainly, it is an assault on reason that in the name of scientific exploration, the United States Administration should spend a small fortune on NASA's extensive schemes while denying much more sober schemers their much more modest requests. This is the point which the Space Science Board at the National Academy of Sciences made last year.

What is to be done? How is NASA to find some way of making peace with the scientific community? At this stage in its fortunes, the best course would be to go back to the beginning and to devise some way of building into the machinery for forward planning in NASA some method of relating what it calls scientific exploration to the needs of scientists. Ostensibly the Scientific Advisory Board which NASA maintains is meant to accomplish precisely that, yet the experience of the past few years has gone to show that even where its activities in pure science are concerned it is inclined first of all to define the rocket and its trajectory and then to ask what instruments it would be sensible to put on board. The way out of this dilemma would be to take the radical step of asking that funds for the construction of instruments for scientific research carried out by NASA should be provided by the National Science Foundation, to which investigators in the United States would have to apply just as if they were asking for money to mount instruments on an ocean-going research vessel or in one of the experimental halls associated with the new accelerator in Illinois. Then it would be sure that proposals for space research at present considered in isolation would be judged in terms of cost and likely benefit alongside other proposals for more conventional activities. NASA, no doubt, would scorn such procedure on the grounds that the National Science Foundation has no reason to respond favourably to requests for grants in space research, but NASA should now recognize that if it fails to take the initiative in devising sensible machinery for scientific planning—not just rubber stamping—it will find itself in that trap.

Fishing in Common Waters

OF the obstacles remaining to the enlargement of the European Economic Community by the accession of Britain, Norway, Denmark and Ireland, one of the most unfathomable is the British Government's request that British inshore fisheries should not be included with the territorial waters of other members of the EEC in the common fishing pool. What the British Government would like to see is a preservation of the six-mile limit within which only British fishermen are at present allowed

to fish. Although the British Government followed others in asking, in 1964, for a twelve-mile limit, so many concessions have already been made between the six and twelve-mile limits to other European nations with traditional interests in these fishing grounds that only a six-mile limit can be thought of as a realistic basis for negotiation. As it turns out, however, the retention of even this limit would greatly influence the pattern of fishing around the British Isles. In particular, because of the accidents of

the ways in which small islands are distributed off the west coast of Scotland and Ireland, even a three-mile limit would give British fishermen sole access to areas such as the Minch off the west of Scotland which are not merely rich in productive fisheries but also rare in the north-east Atlantic for the way in which they appear still to support stocks of herring not yet decimated by over-fishing. Obviously, there will be a great deal of rowing in Brussels before this contentious issue is resolved.

The first thing to decide is whether the British Government is more concerned with the preservation of the inshore fishing industry than with the conservation of the stocks of fish in the North Sea and the Atlantic. Both objectives are of course legitimate, but each of them is coloured differently in discussions such as those now taking place in Brussels. So far as the livelihoods of fishermen are concerned, there is a danger that the issue will be clouded by prejudice and the traditional animosity of fishermen for their competitors from elsewhere. The truth is that the value of the inshore catch to British fishermen must be substantially less than the proportion of the product of all the British fisheries caught by vessels less than 80 feet long, 39 per cent by value in 1970. Around the coasts of England and Wales, inshore fishing accounts for less than a fifth and probably less even than one tenth of the total product of fish, for in 1970 boats shorter than 80 feet brought back only 19 per cent of the harvest of fish. Even if inshore vessels from elsewhere in the EEC were so anxious to exploit English and Welsh coastal waters and so able to do so that they managed to take away half the catch at present landed by local fishermen, the sum of money involved is no more than £5 million a year and probably only half as much. The real problem is in Scotland, where the inshore fishery (defined by the 80 feet vessel) accounts for 70 per cent of all the fish landed. Much of this comes from the Minch. The herring fishery, in particular, is also one of the contemporary Scottish boasts, for it has turned out that a small fleet of vessels is able to land more than £4 million worth of fish each year in a manner that suggests that sea fishing as a whole may yet be made amenable to methods of modern management.

What force is there in the contention that this inshore fishery must be protected? As with many of the other questions with which the EEC is concerned, time is the great healer. In the years immediately ahead, it is plain that inshore waters in the south of the British Isles are unlikely to be seriously fished by vessels from elsewhere. Most probably British fishermen have as much to gain as their competitors from an arrangement under which they are able to cross the Channel to the productive fishing grounds off the coast of Brittany, for example. The Scottish problem, admittedly more serious, does require different treatment, if only because of the care with which the Scottish fishery has been built up in the past ten years, and because of the way in which the livelihoods of isolated communities have come to depend upon it. But are these not circumstances in which transitional arrangements, as with agriculture, will provide a sufficiently resilient cushion?

The more serious question concerns the future of the fish in the North Sea and the north-east Atlantic. One of the potential advantages of the EEC is that it does for the first time provide a framework within which a policy can be worked out for the conservation of the com-

mercially important fishing stocks. There is plenty of evidence that fishing is already a powerful restraint on the populations of fish in European waters. Stocks have been declining steadily since the ending of the Second World War and the resumption then of active fishing. The herring shoals have been specially hard hit, with the result that the British herring fishery has been less and less productive over the years. In circumstances like these, it is evidently in everybody's interest that spawning and breeding grounds should be protected, ideally by the enforcement of regulations on net sizes and even close seasons, but sometimes also by the prohibition of all kinds of fishing in some localities. These are the regulations which need working out internationally, on a European basis, and which should then be maintained from year to year as new information about the stocks of fish become apparent. The difficulty is that not enough is known at present about the principles on which European policy to maximize the productivity of the North Sea and the continental shelf can be devised, which in turn implies that there is now a need to coordinate the research programmes of the several countries with fingers in this pie. The hope is that the British questions about the continued protection of British inshore fishing can be made not so much the excuse for an unseemly squabble as an opportunity for a constructive programme of research, development and conservation.

100 Years Ago



*ON THE NECESSITY FOR A PERMANENT COMMISSION ON STATE SCIENTIFIC QUESTIONS**

THE duty of the Government with respect to Science is one of the questions of the day. No question of equal importance has perhaps been more carelessly considered and more heedlessly postponed than this. And now that a hearing has been obtained for it, neither the governing class nor the masses are qualified to discuss it intelligently. The governing class, because it is for the most part composed of men in whose education, as even the highest education was conducted thirty to fifty years ago, science occupied an insignificant place; and the masses, because they may be taken to be virtually destitute of scientific knowledge. Those who wield, and those who confer, the powers of government being alike incapable of dealing with this question, it devolves on another section of the community to urge its claims to attention.

The section qualified to do this is composed of scientific men, properly so called, of professional men, such as engineers, and certain manufacturers who are engaged in applying science practically, and of a limited number of officers in the naval and military services. This section is without much political influence, but its intellectual power is enormous, and this power has never been so strongly exerted, or so decidedly acknowledged, as at the present time.

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OLD WORLD

CHOLERA VACCINE

Cupboard Almost Bare

ALL the cholera vaccine stockpiled by British pharmaceutical manufacturers against emergencies has now been sent to West Bengal. For the second time in less than a year, the call for vaccine has been so great that the principal manufacturers have been left with only the stocks held as an insurance against outbreaks of cholera in Britain and for the use of people from Britain travelling abroad.

Burroughs Wellcome and Company, which last week supplied Oxfam with 500,000 doses of the vaccine and War on Want with 100,000, was unwilling to predict when its contingency stocks could be replenished; a spokesman from the Lister Institute, which provided Oxfam with 358,000 doses, thought it would take months rather than weeks. Cholera vaccine will be available during this period, but it will be in short supply. Neither Burroughs Wellcome nor the Lister Institute has immediate plans for increasing production of the vaccine. Some two million doses are in various stages of production at the Lister Institute's manufacturing laboratories at Elstree, but it may take two months for this volume of vaccine to be processed. At Elstree, it takes three weeks from the time a batch of vaccine is ready to be dispensed until it can be sent out, tested, bottled and labelled.

There is no statutory regulation for the amount of vaccine which manufacturers in Britain must keep in hand for emergencies, a spokesman for the Department of Health and Social Security said last week. There is, however, an understanding between the department and the manufacturers concerned that "adequate" supplies of important drugs are always maintained. The last time that cholera vaccine was so scarce was in September 1970, when the demand from Africa and the Middle East forced Burroughs Wellcome to ration supplies and to reduce a contingency stock of about two million doses almost to nothing. But both the vaccine makers and the charitable organizations concerned to dispense medical supplies seem almost at a loss for words to describe the scale of the present epidemic.

Most countries where cholera is an endemic and seasonal disease are capable of manufacturing the vaccine—in the case of India or Africa, for example, sufficient for their ordinary needs. But in epidemics, production capacity cannot be raised overnight and additional supplies must be brought in from outside. By all accounts manu-

facturers make the vaccine according to demand, holding a small reserve stock ready for the unexpected epidemic. They are quite understandably reluctant to keep large sums of money and storage space tied up in stockpiling vaccine for which there may be no call and which may have to be thrown away. Furthermore, little seems to be known of the properties of cholera virus when held in store. Dr A. F. B. Standfast of the Bacterial Vaccines Department of the Lister manufacturing unit at Elstree this week guessed that, by analogy with other vaccines, the cholera variety might retain its potency for up to three years in cold storage.

In fact, not enough is known about cholera or the mode of action of cholera vaccine. The vaccine is cheap enough—Oxfam's 858,000 doses cost only £20,000—and is made simply by growing two sub-types of the cholera bacterium species *Vibrio cholerae* on nutrient agar for some 20 hours before harvesting the cells and killing them with disinfectant. The dead cells are stored for two to three months during which they lose their initial toxicity. The two sub-types are diluted and combined to give a final vaccine strength of 8×10^9 organisms per millilitre. This combined vaccine is effective against both classical cholera and the more recent and more resistant "El Tor" variety. Field trials suggest that the vaccine is only about 50 per cent effective, however, and that immunity lasts for no longer than six months.

The combined vaccine is tested for sterility and toxicity; potency trials have not, as yet, proved very valuable. Responsibility for field trials of cholera vaccine has, in the past, rested with the South East Asia Treaty Organization cholera research station at Dacca. No reliable news of the fate of the station is known at present.

Cholera may be rampant in the refugee camps on the Indo-Pakistan border, but is there a real danger that the disease may sweep the entire Indian sub-continent and beyond? Fortunately, the answer seems to be no. The World Health Organization (WHO) in Geneva says that shortage of vaccine is not the principal problem in West Bengal. The Indian Government has asked for only 500,000 doses of cholera vaccine, and these have been supplied from WHO stocks manufactured and stored by the Pasteur Institute in Paris. Saline solution and antibiotics are more urgently needed. Cholera can be treated by killing the bacteria with antibiotics such as tetracycline and replacing the body fluid lost through diarrhoea with saline. The WHO has no plans for maintaining larger stocks of vaccine than at present. The chief problems facing the medical teams in

West Bengal are probably the difficulty of mass vaccination and the limited potency of the available vaccine.

Cholera vaccine has been known and used for over a century but progress towards improving the vaccine has been lamentably slow. Dr P. D. Walker, who is in charge of the development of new cholera vaccine for Burroughs Wellcome, suggested two reasons for the delay. First, proper programmes of vaccination are impossible in countries like Africa and India where the true answer is improved sanitation. Second, it is only in the past two years that it has been known that conventional vaccine stimulates active immunity only against the bacterial cells, without interfering with the action of a toxic protein produced by the bacterium. A new mixed serum has been produced which will stimulate antibody production against both factors which has been tested on the only reasonable model for the disease in man, young rabbits, but field trials have yet to be completed. Ironically, these tests were to take place at the SEATO cholera research centre in Dacca, East Pakistan.

TIME SCALES

Now Leap Seconds

FROM the beginning of next year, the complex relationship between Greenwich Mean Time (GMT) and International Atomic Time (IAT) will be altered and simplified, but the basic objective of achieving approximate agreement between GMT (also known as Coordinated Universal Time, UTC) and the rather variable time scale based on the rotation of the Earth will be maintained.

Greenwich Mean Time has been defined in terms of the time measured by the atomic clock at the Bureau International de l'Heure in Paris since January 1, 1958, when the two time scales were synchronized at 0 h 0 m 0 s. But during the thirteen years which have elapsed, International Atomic Time has drawn ahead of Greenwich Mean Time by almost ten seconds. This means, of course, that a definition of Greenwich Mean Time in terms of International Atomic Time requires the inclusion of a continuous retardation factor of about 30 parts in 10^9 if GMT is to be kept within 0.1 second of an Earth rotation time scale. It is also necessary to make occasional step adjustments of 0.1 second to preserve agreement.

The continually changing relationship between GMT and IAT is clearly a disadvantage to those who use GMT for scientific purposes, although tables of data for converting one to the other are readily available. In recognition of this, the International Radio Consulta-

tive Committee (CCIR) recently decided that GMT should correspond exactly to IAT and that whole second adjustments should be made once every year or so to keep GMT in line with an Earth rotation time scale.

A study group set up at the Plenary Assembly of the CCIR at New Delhi in 1970 has now published instructions about the way in which the changes are to be carried out. An adjustment will be made to all GMT time signal emissions on January 1, 1972, so that a GMT time of 0 h 0 m 0 s will correspond exactly to an IAT time of 0 h 0 m 10 s; thereafter "leap seconds" will be inserted or omitted as necessary at the end of a particular GMT month—preferably on December 31 or June 30. From then on, GMT will always be exactly 10 s slow compared with IAT.

A so-called positive leap second will begin at 23 h 59 m 60 s on the last day of the month selected and end at 0 h 0 m 0 s on the first day of the next month; by contrast, if the leap second is negative, 23 h 59 m 58 s will be followed one second later by 0 h 0 m 0 s.

The CCIR study group has also specified how scientific events which occur near the leap seconds should be recorded so that no ambiguity arises. Events during the insertion of a positive leap second (that is between 23 h 59 m 60 s and 0 h 0 m 0 s) will be designated in a manner such as "June 30, 23 h 59 m 60.6 s" and events during a negative leap second will be recorded as, say, "June 30, 23 h 59 m 58.9 s".

One consequence of the new arrangements is that it will be possible to keep GMT accurate only to within 0.5 to 1 second of an Earth rotation time scale, but the ramifications of this are not likely to be serious.

GLAXO AWARDS

Tinker's Pot

THE sixth annual Glaxo awards for British science writers have been won by Mr Jon Tinker, a freelance science journalist specializing in the environment, and Mr Edward Ashpole, freelance science writer for regional daily newspapers. The awards, which consist of Travelling Fellowships worth £500 apiece, will be presented by the chairman of Glaxo, Sir Alan Wilson, FRS, on June 25.

Mr Tinker, who writes regularly for the British weekly science magazine *New Scientist*, is perhaps best known for the publicity he gave to the controversy surrounding the use of the 'Valpona' fly-strip which contains the organophosphorus insecticide dichlorvos.

PEST CONTROL

Four to One Against

THE Overseas Development Administration of the Foreign and Commonwealth Office (ODA) announced last week that, in keeping with the general policy of streamlining government departments, it has merged four of its scientific units to form a single organization called the Centre for Overseas Pest Research (COPR). The units are the Anti-Locust Research Centre (ALRC), the Tropical Pesticides Research Unit, the Tropical Pesticides Research Headquarters and Information Unit and the Termite Research Unit. Dr P. T. Haskell, present head of the ALRC, will be the director of the new unit which will have a staff of about 140. "It has been clear for some time that the four units have been on a convergent course," said Dr Haskell. Ultra-low level spraying has been investigated by two of the units, and the search for new techniques of control, by genetic methods and the use of sex attractants for example, has been duplicated. Although the individual units will continue to work much as before, the merger will improve co-ordination and, with the advantages of the combined labour force, important new fields of work will be developed.

High on Dr Haskell's list is an assessment of the long-term environmental effects of the use of pesticides in the tropics. "All the experts agree that tropical agriculture will not succeed in the next 10 to 15 years without the use of pesticides . . . including DDT," he said. But it is important that safer methods of application are found and it is clear that lack of knowledge of the effects of pesticides, particularly in developing tropical countries, is a significant impediment to safe and efficient planning and development. The second of COPR's new investigations will be to establish whether the various control techniques are producing value for money. There have been occasions when the increased crop yield has been insufficient to justify the control expenditure, but crop statistics are difficult to obtain and new methods for improving their reliability are needed.

COPR's budget will consist of a straightforward pooling of the resources of the individual units. This amounts to about £500,000 of the £5 million which the ODA allocates annually to research from the total of £200 million that Britain spends every year on overseas aid. Universities and other learned institutions claim £3 million of the research funds, and the remainder is shared among ODA's scientific units which include the Land Resources Division and the Tropical Products Institute as well as COPR.

A wide range of pest species is now

included in the new unit's brief. Locusts remain the principal enemy and the battle waged by the anti-locust centre, the largest locust and grasshopper research organization in the world, will continue unabated. The list also includes species of weaver birds (*Quelea*), which are a widespread scourge in African grasslands where, in vast numbers, they cause great damage to cereal crops.

MANPOWER

Counting Learned Heads

THE first thing to say about the report *Qualified Manpower in Great Britain*, published by the Central Statistical Office this week (HMSO, 65p), is that it is four years late. The twenty-two tables, four charts and eight appendix tables are taken from the 1966 Census of Population, and their bearing on the present manpower situation is in doubt. Nevertheless, the Central Statistical Office is right to claim the report is "the most comprehensive study yet produced in this country of people with higher educational qualifications"; it also pays proper attention to the sources of error in collating the statistics.

The report defines three categories of highly qualified manpower—those with a higher degree awarded by a university, those with a first degree or its equivalent and those with other higher educational qualifications not usually obtainable at school. In 1966, total qualified manpower numbered 2,148,380 or 5.68 per cent of the population aged 18 and over. Of this number, 932,200 or 2.4 per cent of the adult population fell into the two higher categories. Only about one quarter of these were women, but they formed the majority of those with qualifications not of a degree level.

Of those qualified at degree level or above, technology led the way with 214,690, followed by social studies with 180,630 and science with 143,000. The largest numbers of those qualified but without degrees fell, predictably, into education and health with 408,740 and 446,170 respectively, representing, chiefly, school teachers and nurses. Analysis of the figures for education and teaching shows that 92 per cent of all those qualified in educational subjects were teachers; rather surprisingly, 40 per cent of all those qualified at the two higher levels in science subjects also fell into this category—in other words, nearly half of all graduates ended up in teaching. The figures for university teachers as a percentage of all teachers qualified in the subject show that health led the way with 26 per cent followed by agriculture with 23 per cent and science with 17 per cent.

NEW WORLD

NASA in Trouble with Congress, Executive, Scientists

by our Washington Correspondent

TEN years ago, on May 25, 1961, President Kennedy launched the Apollo programme to land men on the Moon, and for the rest of the decade NASA never looked back. Priorities for the seventies are not as clear. Space is no longer so fashionable, and NASA has had to retrench on several peripheral undertakings in order to find room within its straitened budget for the shuttle project, a re-usable space vehicle that will carry aloft NASA's major hopes for remaining a visibly significant agency. But the sacrifice of lesser projects has sown discord among the already uneasy alliance of interests on which NASA depends for support.

Scientists, the least important of the agency's constituents, have seen project after project cancelled or deferred, despite the high scientific priority attached to it. The Office of Management and Budget has taken advantage of NASA's retreat to garrotte stragglers, such as the Nerva nuclear rocket programme, which it has been out to get for years.

The strains of the times are also evident in the Congressional committees responsible for authorizing NASA's budget ceiling; the committees have not only lost prestige in Congress and the ability to retain new members, but are also having difficulty in presenting a united front to their parent bodies on the major issues of NASA policy.

NASA's strategy for survival is to push the shuttle programme, keep its head low and pay belated respect to the notion that all kinds of manna in the form of practical and military benefits will fall from the continuance of a manned space programme. The shuttle, for instance, is being stressed as a system for putting weather and other useful satellites into orbit, not as a means for launching men to Mars. NASA has also been forced into military company by accepting the Air Force as a partner in the shuttle enterprise.

With its Manned Orbiting Laboratory cancelled two years ago after an expenditure of \$1,400 million, the Air Force is eager to get back into space and its use of the shuttle (for unspecified military purposes) is expected to be as frequent as NASA's. Air Force patronage is in fact essential if the shuttle is to receive enough work to make it economically viable, which may be one good reason why last January, after long resistance, NASA altered the

design specifications of the shuttle to bring it closer to the Air Force's desire. The Air Force keeps tabs on the shuttle through a joint Air Force-NASA Space Transportation Committee which was set up in February last year.

Although the Department of Defense will be a principal user of the shuttle, it has not contributed to its development costs. NASA has had to finance the project alone and the burden is made no lighter by the Office of Management and Budget whose practice is to grant NASA half the shuttle money it asks for each year. For fiscal 1971, NASA asked \$170 million for the shuttle and got \$80 million; for 1972 it asked \$190 million and was permitted to request only \$100 million from Congress, enough to start developing the main engine of the shuttle but not the frame of the vehicle. At present, NASA estimates the total cost of developing the shuttle will amount to some \$9,000 million, or nearly half the cost of Apollo.

Even the \$100 million request now before Congress may present too high a profile for NASA's good. The House Committee on Science and Astronautics, charged with setting an upper limit to NASA's expenditures—the House Appropriations Committee may then grant any sum up to this maximum—decided in April to give NASA an extra \$25 million for the shuttle, making a total of \$125 million. The committee also awarded increases for other programmes that made NASA's authorization up to \$3,434 million, or \$163 million more than the sum requested by the Administration. But the committee is a traditional friend of NASA and for the last three years has regularly raised the agency's official authorization.

Last week the authorization bill was passed by the House almost without incident. An amendment to delete funds for the shuttle, on the grounds that social ills needed the money more, was offered by Mrs Bella Abzug, a colourful Representative from New York, but defeated by voice vote. The shuttle's hardest hurdle, however, is in the Senate, where last year Senator Proxmire and allies came within four votes of scuttling it.

Having tasted the blood of the SST (a venture NASA insists is in a quite different category) the Senate foes of aerospace spending have already opened hostilities against the shuttle. Last

month, Senator Mondale made public a report prepared for the Air Force by the Rand Corporation in October last year which predicted that over the next twenty years the shuttle would not be any cheaper than conventional ways of getting into space; moreover, it would entail an increase in the total NASA budget to a peak of more than \$7,000 million in 1975—more than double its present size.

NASA supporters have been quick to discount the Rand study, saying that it is based on data which are two years old, that NASA has in any case never sought to justify the shuttle on purely economic grounds and that the report represents only the views of its authors, not the Rand Corporation. Be this as it may, the report has done no good to the shuttle's chances of getting through the Senate.

Another blow to the shuttle's chances in the Senate comes from budget cuts on the Nerva nuclear rocket programme, which, ironically enough, were made in order to conserve funds for the shuttle. NASA and the Atomic Energy Commission (the programme is a joint venture between the two agencies) are asking Congress for only \$17 million this year, which is barely enough to keep the project ticking over. This cutback has antagonized NASA supporters in Congress, some of whom have in the past fought bruising battles with the Administration to keep the programme alive. Moreover, some \$1,400 million has been invested in the programme since it began ten years ago and its cancellation at this stage would be an embarrassment to the committees which have urged its funding.

Another undesirable aspect of the cutback, from NASA's point of view, is the displeasure it has caused two of the agency's principal supporters in the Senate, Clinton P. Anderson and Howard W. Cannon, in whose states (New Mexico and Nevada respectively) important segments of the Nerva programme are situated. Anderson is chairman of the Senate Committee on Aeronautical and Space Sciences, which handles NASA's authorizations, and Cannon, because of Anderson's advancing years, has recently carried much of the burden for defending NASA on the floor of the Senate.

A meticulous analysis of the programme in a recent issue of *National Journal* quotes a Senate aide as saying of the Nerva cutback, "This is one of

the stupidest decisions NASA has ever made. Nerva has more backing in Congress, probably, than any other single space program. Now they're expecting guys like Anderson and Cannon to go in and fight like hell for the shuttle when they've just kicked them in the teeth on Nerva."

Anderson and Cannon have not taken their kick in the teeth lying down. Last month the Senate Committee passed on to Congress an authorization bill for NASA that increased the requested budget for Nerva by \$38 million. (The House Committee, also annoyed by the cutback on Nerva, had raised the budget by \$35 million.) Unlike the House Committee, however, which has shown no compunction in going above the President's request, Anderson's committee has traditionally followed the Administration's overall guideline. The extra funding for Nerva had to come from elsewhere in the NASA budget and the committee took \$16 million of it from the agency's provision for salaries and docked \$20 million from the \$30 million requested for the Grand Tour of the outer planets. The committee followed the Administration in authorizing \$100 million for the shuttle, giving a total budget figure almost exactly in line with the President's request.

NASA will face the most determined assault on the integrity of its budget when the Anderson committee's bill comes on to the floor of the Senate. The dissensions raised by the Nerva programme have undermined the unity that Anderson has until now preserved on his committee, and which was an important factor in preserving NASA's budget from raids made on the floor of the Senate. At worst, the sacrifice of the Nerva programme could thus be fatal for the future of both the shuttle and NASA. Why did the agency commit so gross a tactical error? According to the *National Journal* article, the slip was made last September in the annual sparring match with the Office of Management and Budget. Told to reduce an original budget request of \$3,700 million, NASA came back with a \$3,200 million budget in which the agency's share for Nerva, originally \$50 million, bore some part of the reductions.

This decision may have seemed reasonable enough to NASA planners, since the Nerva engine can only be flown after launch by the shuttle, to which it was logical to give priority, and in any case NASA has not yet assigned any particular missions to Nerva; even with the Grand Tour, the earliest mission in which a nuclear rocket might be used, the advantage of reduced flight time offered by a nuclear engine is outweighed by the proven reliability of chemical rockets.

Reasonable as the reduction in the Nerva request may have seemed, it was a fatal error. Budget Bureau officials had for years tried to wield their knives on the Nerva programme, often with the support of the reigning science adviser (though this year the new science adviser, Edward E. David, apparently supported the programme); but each year NASA fought tooth and nail to retain the programme, sometimes even by carrying the dispute directly to the President. This year, at NASA's first sign of weakening, the Office of Management and Budget plunged in the knife and cut out all funds for Nerva. Realizing its error too late, NASA pleaded for its restoration and got back only a token amount, acquiescence in which has left the agency's Congressional allies in the lurch.

The cutback on Nerva is not the only shift in priorities that has annoyed NASA's natural allies. Last year the halting of production of Saturn V rockets and cancellation of the final two Apollo shots, both of which were economy measures taken to make room for expenditures on the shuttle, antagonized traditional NASA supporters. Seven members of the House Committee on Science and Astronautics expressed disagreement at shutting down the Saturn V production line in view of the agency's intention to start it up again in 1976. The scientific community was particularly upset at the failure to extract the maximum benefit from the investment in the Apollo programme by scrapping two of the last and potentially most productive Moon landings.

Other wasteful economies forced by the shuttle include the failure to provide back-up vehicles for expensive missions. This policy was brought into prominence by the loss of an orbiting telescope (OAO-B) last November and of the first of the two Mariner spacecraft launched towards Mars last month. The OAO-B failure represented the loss of a \$100 million investment, yet the cost of a replacement vehicle would have been about \$50 million. Similarly the abortive Mariner 8, costing \$77 million, could have been replaced for \$24 million. Departure from the usual policy of providing back-ups for unique missions has been severely criticized by members of the House Committee on Science and Astronautics. In passing on to Congress the NASA authorization bill two months ago, the committee expressed its dissatisfaction at NASA's failure to replace the two orbiting telescopes that failed. Over the years the committee had been assured by NASA that each of three missions was unique and essential. The committee reluctantly concludes, the authorization report declares,

"either that Congress was misled by that testimony, or that NASA management is prepared to abandon a huge investment in an established project in order to embark upon expensive new ones".

If Congress is upset by the present course which NASA has taken, so too is the agency's most negligible and on the whole most neglected constituency, the scientific community. NASA has paid almost no serious attention to the list of scientific priorities drawn up last summer by the Space Science Board of the National Academy of Sciences (see *Nature* **230**, 142; 1971). The academy board stated that on its present budget for unmanned space programmes, NASA should not undertake the Grand Tour mission since it would crowd out smaller projects.

Asked by the House space committee why it had ignored this advice, the agency, in a careless or wilful misunderstanding of the board's position, replied that its budget had increased to the level the board said would allow for the Grand Tour mission. In fact the increase this year is largely for the Viking mission to Mars and the residual budget is of the size that, in the academy board's opinion, does not permit the Grand Tour. Two other recommendations ignored by NASA were a plea not to cancel the last two Apollo missions and a strong suggestion that the support of balloon and rocket research should be doubled. The latter recommendation has at least been heeded by the House space committee which has authorized an extra \$2 million above the \$18 million requested by NASA and the Administration. Ironically, the academy board's reservations on the Grand Tour, though without influence on NASA, may have carried some weight with the Senate space committee when it was searching for funds to transfer to Nerva. As far as scientific benefits are concerned the Grand Tour has much to offer, if less than other projects; Nerva has next to nothing. As to the shuttle itself, a panel of the President's Science Advisory Committee gave tentative support to the project in 1969, and Charles H. Townes, chairman of the space science board, commented favourably on it in a letter last year to a member of the House Science and Astronautics committee. But the Space Science Board in its report issued last March states categorically that "space science and applications by themselves are insufficient to justify the cost of developing the shuttle".

The positions taken by the House and Senate authorization committees are subject to modification at later stages of the appropriations process. The budget cuts made by the Senate Space Committee in the Grand Tour mission, for example, may be re-

stored in whole or in part in later conference with the House. But the Grand Tour is a bagatelle compared with NASA's ambitions for the shuttle.

In staking its future on the shuttle, perhaps a necessary move, NASA has made a devil's pact with the military, ignored the advice of the scientific community and risked antagonizing its supporters in Congress by sacrificing peripheral projects. The gamble is a dangerous one, but at least if it fails NASA will end with a bang, not a whimper.

ENERGY POLICY

Power Without Pollution

THE White House announced last week a package of proposals to increase the power available in the United States and at the same time a number of regulations and declarations of intent that may avert the criticism of those who hold that power means pollution. The most conspicuous beneficiary of President Nixon's power package will be the research and development programme of the Atomic Energy Commission which may ultimately lead to a commercially viable fast breeder reactor—the difficulties so far have been not technical but administrative. The other chief contender for extra government support, the thermonuclear fusion programme, will plainly have to take a back seat for the time being—the support in this year's budget amounts to \$27 million, much less than the enthusiasts would ask for but probably enough to keep the pot bubbling until the late 1990s, when fusion reactors may become working instruments.

The immediate cause of President Nixon's new programme, which seems to have been given not merely the blessing but the active support of Dr Edward David, the Science Adviser at the White House, is the impending shortage of energy in the United States. In spite of the economic recession of the past year, the demand for energy has grown steadily and, since 1967, at a pace that has taken the prophets by surprise. Among the symptoms of shortage in the past few weeks have been the mutterings by Consolidated Edison in New York that the city will have to take steps to halt the growth of its population if the company is to be able to maintain a supply of electricity to Manhattan.

Under the new proposals, expenditure in the coming financial year on the development of fast breeder reactors will be increased by \$27 million, an increase of some 25 per cent. Although the President asks that the culmination of the programme should be "the construction of a demonstration plant of some 300 to 500 MW", he also says

that there are "major technical and financial obstacles" to be surmounted. It has been known for some time that most of the obstacles are financial. Too many of the companies in the field are aware of how badly they have burned their fingers with the now conventional types of nuclear reactor, and some of them would like the chance to make a profit on the designs they are now bringing into commission before embarking on newer and more hazardous ventures. This is why the new power programme also allows for an extra \$50 million of Federal money to be spent on the demonstration plant, intended as a collaboration between a utility company, one or more manufacturers and the government in which the utility will pay the going rate for whatever electricity is produced and the AEC will commission the manufacturers to build on a fixed-price contract.

The provisions for extra help for the breeder reactor programme will be widely interpreted as a success for the AEC's insistence in the past year that breeder reactors would be an essential part of the power supply system in the United States in the 1980s but that it would necessarily be a long job to bring this development to fruition. In this respect, the US AEC is much less optimistic than its equivalents elsewhere about the ease with which breeder reactors can be constructed. President Nixon last week went out of his way to say that breeder reactors could be not merely cheap but also proof against the discharge of radioactivity or of waste heat and even that "the breeder reactor will soon become a key element in the national fight against air and water pollution".

The other components of the package announced on June 4 are a programme of research on coal gasification as well as one for coal liquefaction. Magnetohydrodynamic power cycles are to be investigated more fully, as are methods of transporting electricity in bulk by cables underground. Even solar energy will get some extra support, as will controlled thermonuclear research—an extra \$2 million in the current financial year.

Administratively, the United States Government can do a great deal by licensing the exploitation of natural resources on land which it controls and to this end it has agreed to the experimental leasing of a tract of oil shale in the Rockies; ultimately the United States might expect to obtain 50,000 million tons of petroleum from its own oil shale deposits. The government is also planning to lease more territory for exploitation in the continental shelf and also to lease rights for the exploitation of geothermal energy.

How is all this to be accomplished?

It is intended to set up a new Department of Natural Resources to co-ordinate research, development and exploitation of energy resources. The intention is that the Atomic Energy Commission should remain intact but that the planning of its research should again be coordinated by the Department of Natural Resources.

INTERNATIONAL COMPETITION

Writing to Win

WORKING scientists with a book inside them and competitive instincts now have the choice of two writing tournaments to enter. In addition to the Adam Hilger Prize for 1972, announced this year (see *Nature*, February 5, xiii; 1971) Butterworths of London propose to celebrate a quarter century of science publishing by awarding a scientific fellowship for authors. The winners will receive a cash prize—£500 from Adam Hilger or £750 from Butterworths—and will have their manuscripts published. The route to the top in each competition is quite different, however, and potential competitors would do well to study the form carefully before placing their bets.

Adam Hilger Ltd, a subsidiary of Rank Precision Industries, is asking for previously unpublished books or monographs, in English, but on topics restricted to physical and chemical aspects of astronomy or geology and the analytical aspects of pollution. The adjudicating panel will consist of Professor H. Kaiser, Dortmund, Germany, Professor L. H. Ahrens, Capetown, South Africa, and Professor A. J. Meadows, Leicester, England. Entrants will have a reasonable time to complete their manuscripts; for the 1972 prize, entries must be received before November 1972, and the judges will give their decision early in 1973.

On the other hand, Butterworths are asking only for synopses of the proposed manuscript and the winner will be chosen on this basis. Entries must be submitted by October 1971, and the judges will be Professor Sir Harold Thompson, Oxford, Professor D. H. R. Barton, London, Mr J. A. Charles, Cambridge, Professor F. C. Frank, Bristol, and Professor J. L. Harley, Oxford. They will make their decision in the same month. Unlike Hilger's, Butterworths will accept entries on any science topic and, with an eye on sales, are anxious that prospective authors should not pick too erudite a title.

Literary competitions of this kind are a new venture for both companies and indeed for British science publishers in general. Butterworths are anxious to establish their competition on an annual basis, and Hilger's on a two-yearly schedule.

NEWS AND VIEWS

Gamma Ray Stars must be Variable

To many astronomers the article on page 372 of this issue of *Nature* is another example of how feckle their colleagues in gamma ray astronomy can be. Some years ago, the collaboration between Case Western Reserve University and the University of Melbourne produced the first evidence for the existence of a point source of gamma rays, Sagittarius γ -1, but nobody has been able to confirm it. At the same time the Case-Melbourne group reported that in the same experiment they were unable to verify the diffuse flux of gamma rays coming from the plane of the galaxy observed from the third Orbiting Solar Observatory. Gamma ray astronomy, to put it bluntly, is suffering from problems of reproducibility. That is why the latest contribution from the Case-Melbourne collaboration in this issue in which two more point sources of gamma rays are reported will be looked at quizzically in observatories around the world.

Briefly, what the Case-Melbourne group have done is to combine the data from the two balloon flights during which the Sagittarius source was detected with a third flight that was also carried out from Australia. This approach has revealed the two new sources, each at about four standard deviations above the background counts. As was the case with the discovery of the Sagittarius source, signals that barely stand out from the background when each flight is considered on its own take on a new significance when the slight excesses of counts are found to occur at the same position on the sky during each flight. But what settles the veracity of the new sources for the experimenters—and may well be what will convince others as well—is that the positions of the two new sources overlap those of two X-ray sources which are known to have spectra extending to high X-ray energies. And the gamma ray fluxes seem to be of the magnitude expected from a straightforward extrapolation of the X-ray spectra.

But the sceptics will say that in gamma ray astronomy signals that are only four standard deviations above the background are not good enough. After all, one of the characteristics of gamma ray astronomy seems to be that the background can show sporadic variations that in the past have confused the experimenters.

Is this the reaction that this week's article should meet? In spite of the uncertainties—indeed for the same reasons to do with reproducibility that the three gamma ray point sources are likely to be regarded as questionable—there is another interpretation that the Case-Melbourne group will be impressing on people in the coming months. This is that gamma ray sources are as variable as some X-ray sources have turned out in the past few years to be. What is causing the gamma ray variability—some kind of flaring perhaps—is as uncertain as the explanation of the X-ray variability, but with the Case-Melbourne group canvassing support for a link between the two types of object this explanation now seems plausible.

What about the other outstanding problem that the irreproducibility of the gamma ray results has turned up—the existence of the diffuse gamma ray emission coming from the galactic plane and the galactic centre? Once

again in the latest article the Case-Melbourne group are in danger of becoming heretics for failure to report evidence for the galactic source. How could experiments that are capable of revealing point sources of gamma rays miss the diffuse emission from the galaxy? The answer here now seems to be that the galactic emission may be nothing more than the summation of emission from objects such as the two new sources reported this week, for the two sources are in the galactic plane, and the X-ray sources with which they have been associated belong to the class of X-ray objects that form a concentration in the direction of the galactic centre. Maybe contributions to the gamma ray observations are coming from more of the dozen or so X-ray sources in this concentration that seems somehow to be associated with the galactic centre. Indeed, the broad acceptance angle of the detector on the Orbiting Solar Observatory that first picked up the galactic emission, $\pm 15^\circ$, suggests that the detector was smearing out point sources that the more precise balloon experiments are now able to resolve.

That does not explain why the emission from the gamma ray sources so far identified is still not altogether enough to produce the flux as measured by the Orbiting Solar Observatory. Once again the Case-Melbourne group will be tempted to invoke variability of the sources—there is a factor of two or three in intensity to be accounted for to explain the diffuse emission from the galactic centre fully, but greater variability may be needed to explain the emission from other directions.

The next major step on the observational side of gamma ray astronomy is still some months away, when the next in the series of Small Astronomy Satellites, this time devoted to gamma ray astronomy, will be launched. Everybody hopes it will be as successful as the first in the series, launched late last year for the benefit of X-ray astronomers. Yet it looks as if there is going to be a place for balloon experiments like those being carried out by the Case-Melbourne group for some time to come. The way in which the satellite will continuously scan the sky, rather than lock onto a particular source, will make it better as a mapping instrument than as an instrument which will throw more light on the way in which gamma ray sources vary in intensity.

And indeed large-scale variability over short intervals of time is not being ruled out by high energy astronomers at present. Whether a study of the variability can throw more light on the nature of the sources of radiation in the direction of the galactic centre is an open question, but the news this week that the X-ray sources may well be detectable over three decades in energy may be the beginning of detailed studies of their mechanisms. It now seems clear enough, for example, that these X-ray sources are not like Scorpius X-1—the source that has been identified with an anomalous blue object—nor are they, like many other X-ray objects, supernova remnants. With there being feeling that the unusual X-ray sources must have something to do with the other goings on at the galactic centre, anything that gamma ray astronomy can do to help is welcome.

PROTEIN EVOLUTION

Is Selection the Cause?

by our Population Genetics Correspondent

It is becoming something of a dogma in population genetics that changes in particular amino-acids in a protein seldom affect an organism's chances of survival: such changes are thought to be selectively neutral. Kimura and Ohta (*Nature*, **229**, 467; 1971) have strongly upheld this view.

During evolution, particular proteins have undergone considerable changes in the amino-acids of their polypeptide chains. These evolutionary changes can be observed by comparing the same protein in different organisms. For example, the α and β chains of haemoglobin can be compared in several different mammals. When such proteins are compared in two species, the mean number of amino-acids that have been substituted for others can be calculated for the period since the species were separated in evolution. Kimura (*Proc. US Nat. Acad. Sci.*, **63**, 1181; 1969) has calculated this number for comparisons between different vertebrates; he suggests that the substitution of one amino-acid for another in a particular protein has occurred at a more or less constant rate in the history of the vertebrates.

This fact fits the simple theory that new mutations causing amino-acid changes spread through populations chiefly by the purely random process known as genetic drift. No selection need occur. On this theory the rate of substitution of one mutation for another is simply equal to the mutation rate. If the mutation rate has been constant throughout the history of the vertebrates, then so will be the rate of substitution of amino-acids.

Kimura has also shown that this theory will explain the common occurrence of enzyme polymorphisms. The average number of individuals who should be heterozygous for different variants of an enzyme can be calculated. The calculations are in agreement with the observed values. And by assuming there is no selection, the large proportion of loci that are polymorphic in their proteins contribute nothing to any possible "genetic load" on the population: the proportion who die as a result of selection is very small.

Thus the data on enzyme polymorphisms and the rate of amino-acid substitutions are at least consistent with the hypothesis that most of these protein differences are selectively neutral. This is an argument based on a general agreement between the hypothesis and the sum of the observations. But in strict logic, a negative hypothesis must be proved to be false; overall agreement with some data cannot prove it

is true, for another theory might provide an equally good agreement.

It may be wondered if the present views on protein polymorphisms are based on arguments that are rather too similar to the views of about twenty years ago on visible polymorphisms in morphological patterns—such polymorphisms as the differences in the colours and banding patterns of the snail *Cepaea nemoralis*. At that time it was a common view that differences in the frequencies of the alleles in different populations were simply caused by the effects of genetic drift, for the overall distribution of gene frequencies in different populations more or less follows the theoretical distribution of gene frequencies when there is no selection. But whenever selection was looked for in particular populations and environments, it was found to be the chief factor that determined the gene frequencies. It was only the sum of the data from all the populations that gave the appearance of an agreement with the hypothesis of genetic drift. A similar argument was applied to the blood groups, but again evidence of selection was quickly found.

Will the different variants of a protein also be found to be the subject of strong natural selection when particular populations are studied? It could be so. Yarrow and Kojima (*Genetics*, **57**, 677; 1967) obtained evidence for a strong frequency-dependent selective

effect on two variants of an esterase in *Drosophila melanogaster*. The esterases were classified electrophoretically into fast and slow types. In population cage experiments, the esterase at the lower frequency always increased in frequency. The selection was shown to be frequency-dependent, the rarer allele having the advantage. Kojima and Tobari (*Genetics*, **61**, 201; 1969) obtained more evidence of frequency-dependent selection for two types of an alcohol dehydrogenase. Koehn and Rassmussen (*Biochem. Genet.*, **1**, 131; 1967) and Koehn (*Science*, **163**, 194; 1969) obtained very clear evidence of selection in natural populations for fast and slow variants of an esterase in the fish *Catostomus clarki*. The selection was associated with enzymatic activity. That variant of the enzyme which was more common in the southern, warmer areas had a higher activity at higher temperatures. The other variant had a higher activity at lower temperatures. In experimental populations of *Drosophila melanogaster*, Gibson (*Nature*, **227**, 959; 1970) found temperature sensitive variants of alcohol dehydrogenase with selective effects.

Koehn, Perez and Merritt (*Amer. Nat.*, **105**, 51; 1971) have now obtained evidence of selection affecting certain esterase loci in another fish *Notropis stramineus* which lives in the Kansas river. Populations were sampled along the river during a period of three years.

Quarrying for Fragments

RECENTLY, Allet and Spahr showed that the 50S ribosomal subunit of *Escherichia coli* could be hewn in half with pancreatic ribonuclease. The two pieces only dissociated, however, when some of the proteins were extracted with salt, and the implication was that it was interactions between proteins that kept the fragments cemented together. Now Brimacombe and his co-workers, in an article in next Wednesday's *Nature New Biology*, show that at least one defined fragment can also be quarried out of the 30S subunit, though with much more extensive destruction of the rest of the particle.

On digesting the native 30S subunit with T1 ribonuclease two new high-molecular weight components appear in polyacrylamide gel electrophoresis. There is also a smear of aggregated subunits. Radioactivity measurements in the gel patterns produced from ribosomes, labelled in both the RNA and protein, show that all the components in the mixture have much the same protein:RNA ratio, and are thus all true nucleoproteins. The bands were isolated from the gels and treated with detergent to extract the proteins, which were then examined in a standard gel

electrophoretic system. The protein content of the band in the position of residual 30S subunit that survived digestion and of one of the new bands was similar to that of the native 30S ribosome, but the other band contained only a few of the twenty proteins, the rest being completely absent. The pattern of proteins, moreover, was constant across the electrophoretic zone of the component, which is good evidence that this is indeed a unique homogeneous nucleoprotein. The other nuclease-generated band is evidently a mixture of products.

The isolation of an intact, defined fragment of this kind promises well for the degradative approach to ribosomal structure. Brimacombe and his colleagues clearly have much work before them, for they will wish to identify the proteins of their fragments, and see where they belong, in terms of the categories defined by Nomura's work on reconstitution, and establish which part of the RNA chain it is with which they are associated. After this perhaps it will prove possible to achieve controlled degradation to progressively smaller fragments, containing only single proteins.

The frequencies of the alleles at the main esterase locus remained constant throughout the period in all the areas sampled. Apparently there is a balanced polymorphism of the esterases. This could be explained if the heterozygote were fitter than the two homozygotes, but in the data on *Notropus* the heterozygotes are at a lower frequency than they should be according to the Hardy-Weinberg law which assumes random mating and no selection. If the heterozygotes were the fittest genotypes, their frequency should be greater than that predicted by the Hardy-Weinberg law, not less. It is most unlikely that the heterozygotes should be less fit than the homozygotes, for this is an unstable situation from which one of the alleles must rapidly be eliminated—very rapidly in view of the large selective coefficients which would have to be about 30 per cent to maintain the observed frequencies of the genotypes.

A deficiency in the number of heterozygotes can be produced if the samples are taken from a number of separate populations with different gene frequencies. Thus any assemblage of populations in the process of divergence will necessarily show an overall deficit of heterozygotes. But in the data on *Notropus*, the variance in the gene frequencies is very small and this effect can be shown to be insignificant. The variance in gene frequencies, however, was calculated from the gene frequencies of the different samples. If each sample consisted of individuals of the partly isolated subpopulations, then the true variance could be large and produce a large deficit of heterozygotes.

Koehn, Perez and Merritt's data are most easily explained by frequency-dependent selection though this is a possibility they do not consider. At the equilibrium point, the number of heterozygotes can be in deficit as shown by Clarke and O'Donald (*Heredity*, **19**, 201; 1964). If so, this would be another esterase polymorphism to be maintained by this kind of selection. Certainly the selective forces must be large to produce the genotypic frequencies found in *Notropus*. It is interesting that although the data on enzyme polymorphisms show an overall agreement with the theory of genetic drift, yet all those polymorphisms that have been studied in detail seem to be under the control of strong selective forces.

TUMOUR VIRUSES

Fixing Transformation

from our Cell Biology Correspondent

As long ago as 1966 Todaro and Green reported a series of elegant experiments which showed that stable transforma-

tion of mouse 3T3 cells by Simian Virus 40 depends on the cells dividing at least once after infection. The fixation of transformation apparently requires some cellular function or state which is not expressed when cells are resting in the G1 phase of the cell cycle, but is expressed either during DNA replication or during the G2 phase. Furthermore, both SV40 and its close relative polyoma virus can, on infection, induce resting cells—both permissive cells which support the complete replication of the virus and non-permissive cells which are potentially susceptible to transformation—to begin to replicate their DNA. Todaro and Green's experiments were not designed to test whether the cells which become stably transformed by SV40 arise from those cells in an infected population which are induced by the virus to replicate their DNA, but Fox and Levine (*J. Virol.*, **7**, 473; 1971) have now directly tested this proposition.

To determine whether that fraction of 3T3 mouse cells which are induced to replicate their DNA after SV40 infection give rise to the stable trans-

formants, they infected confluent monolayer cultures with high multiplicities of SV40 (250 plaque forming units per cell). While monitoring the induction of DNA synthesis with suitable labels, they partially separated through Ficoll gradients up to 60 per cent of the cells induced to synthesize DNA by 24 hours after infection; these dividing cells are, of course, larger and faster sedimenting than the non-induced non-dividing cells. Once separated, the transformation frequencies of the two populations were simply measured and sure enough the frequency of transformation in the dividing cell population was found to be 40–57 per cent compared with some 7–12 per cent in the slower sedimenting, non-induced populations.

This result neatly confirms and extends Todaro and Green's original observation; but why cell division is necessary for the stabilization of transformation remains an enigma. It may be that the viral genome can only integrate as the host cell's DNA replicates but, alternatively, the fixation of transformation may depend on a cell or viral function which is only

Reducing the Cost of Drag

It is well known that a small amount of additive in a solvent in turbulent flow can reduce the pressure drop (drag) without changing the rate of flow (the "Toms effect"). The additives are either naturally occurring macromolecular substances (for example, some polysaccharides) or man-made polymers (for example, polyacrylamide and polyox); the molecular weights of effective additives are between 1 and 10 million but their concentration in solution only needs to be minute (10 p.p.m. by weight).

Obviously there are many industrial situations involving turbulent flow where considerable economic advantage results from reducing the drag. The drag on ships at high speed, for example, has been reduced by as much as half by ejecting polymer solutions into the stream at several points along the length of the ship; unfortunately, however, the solution is lost and the cost of this loss is not necessarily less than the cost of the fuel saved because of the reduction in drag.

Drag reduction in long pipelines is clearly of great economic importance and most of the work on drag reduction has been done in pipe flow (for example, H. C. Hersey and J. L. Zakin, *I & EC Fundamentals*, **6**, 381; 1967).

The amount of polymer lost can be reduced by pulsative ejection and in next week's *Nature Physical Science* J. Wu reports his finding that polyox retained on the surface of a solid plate

is an effective drag reducer while it is being washed away. This could be a further factor in deciding on the optimum rate of ejection for maximum economic advantage. Wu's finding is in keeping with the well known difficulty of making reproducible experiments with polyox solutions particularly in metal apparatus; several applications of solvent are required to clean polyox off metal walls so that no effect is observed in the flow of a control liquid (usually the solvent).

The amount of drag reduction is a function of several variables such as the concentration of polymer in the solution, the size, shape and flexibility of the polymer macromolecule and the physical dimensions of the pipe or other physical obstacle in or around which the flow occurs. Several attempts are now being made to account for the mechanism of drag reduction both from the molecular viewpoint and macroscopically from suggested equations of state for the fluid. When a fluid passes an obstacle in turbulent flow there is a thin layer of fluid at the surface of the obstacle in which the flow is laminar (the viscous sublayer); the drag is a function of the thickness of this sublayer and there is experimental evidence to show that polymer additives increase its thickness. There are also indications that the intensity of turbulence and the frequency of some turbulent flashes are reduced in polymer solutions.

expressed during the S or G2 phases of a cell cycle. Deciding between these alternatives will no doubt take all the ingenuity Levine and his colleagues can muster.

Presumably both SV40 and polyoma virus have acquired during evolution the capacity to induce the replication of the DNA of the cells they infect because these viruses rely on cellular DNA replication machinery for the replication of their own genomes. Because most cells in an adult animal are not dividing, a viral gene which can push a cell into division would confer great selective advantages to the virus, for it would greatly increase the range of cell types in which the virus could replicate. But the question of which cellular enzymes are essential for the replication of these viral genomes is likely to remain unanswered until a replicative complex which supports the replication of SV40 or polyoma virus DNA *in vitro* is isolated. And the technical difficulties and uncertainties which face anybody trying to isolate such replicative complexes from, for example, mouse cells infected by polyoma virus can be gauged from the report of Green, Miller and Hendler (*Proc. US Nat. Acad. Sci.*, **68**, 1032; 1971).

Using methods basically similar to those which Green and his co-workers exploited to isolate a complex of bacteriophage λ DNA and DNA polymerase from *Escherichia coli*, this group has fished out of infected mouse embryo cells a complex of polyoma DNA and protein which sediments at about 55S. After long labelling periods the labelled polyoma DNA molecules in this complex are covalently closed circles whereas after short pulses label is found in nicked polyoma DNA molecules. But the complex does not support DNA synthesis *in vitro*, and as Green *et al.* fully appreciate, in spite of its homogeneous sedimentation profile, the complex might be nothing more than an aggregation artefact produced by their extraction procedure.

FIELD REVERSALS

Details of Transition

from our Geomagnetism Correspondent

THE discovery that in the past the Earth's magnetic field existed in both normal and reversed states, and has frequently flipped from one polarity to the other and back again, poses the question of exactly what happens during a transition. It is, in fact, a very difficult problem to solve. The only way of investigating field reversals experimentally is by means of palaeomagnetism; but in this case everything

depends upon finding the right rocks of the right ages in the right places. All the available evidence suggests, for example, that any given field reversal takes place in less than 10,000 years, which means that the proportion of igneous rocks actually magnetized during a transition is not likely to exceed a few per cent. The chances of being able to investigate a transition using a suite of igneous rocks are thus very small. Nor are sedimentary sequences necessarily suitable. To be sure, sediments have the advantage of being continuous in time; but the accumulation rates of sediments are usually so slow that field changes are smoothed out and high resolution is therefore difficult to obtain.

In spite of these problems a few transition studies have been carried out on both lava flows and sediments. To add to these, however, Dunn *et al.* (*Science*, **172**, 840; 1971) have now carried out a full field transition investigation which ingeniously avoids both the discontinuities inherent in lava suites and the poor resolution inherent in sedimentary sequences. What they have done is to examine a single, igneous intrusive body which has cooled comparatively slowly from the outside. The theory behind it is that if such a body cools slowly enough (that is, slowly for igneous rocks) a large time-span of the ancient geo-

magnetic field will be recorded continuously as the Curie point isotherm slowly moves further into the intrusion. In other words, the intrusion should contain a record of time changes of the Earth's magnetic field from the outside towards the interior.

The particular body in question is the Tatoosh intrusion in Mount Rainier National Park, Washington, a geological feature many miles in diameter. Dunn and his colleagues concentrated their attention on the southern part which was intruded at a shallow depth; in particular the Nisqually Valley region where the intrusion is a medium-grain granodiorite with very little variation in either petrology or intrinsic magnetic properties. This latter point is important, of course. The discovery of a polarity change within a single rock body inevitably leads to a suspicion of self-reversal rather than field reversal. In this case, however, self-reversal seems unlikely. For one thing the distribution of normal, reversed and intermediate samples within the intrusion is not random but follows a pattern which is entirely consistent with the known cooling history of the body. Second, tests show that the intermediate samples contain a weak field magnetization which exists throughout the whole blocking temperature range and is not attributable to the combined effect of normal and reversed magnetizations in

Neutron Solidification Pressure

THE identification of pulsars as rotating neutron stars has given new impetus to the study of matter at very high densities. Since Malvin Ruderman (*Nature*, **223**, 597; 1969) first pointed out that the crusts of neutron stars would be solid as a result of strong coulomb forces at high densities, increasing attention has been paid to the exotic properties which matter in extreme regions of pressure and density might display. In the picture which has emerged from this work a large neutron star has a crust of relativistic degenerate electrons and neutron rich nuclei arranged in a solid lattice. Underneath there is a mantle of superfluid matter consisting almost entirely of neutrons. Still deeper in the core of the star is a barely understood region where strange particles and mesons exist in significant proportions.

In the next issue of *Nature Physical Science*, P. W. Anderson and R. G. Palmer of the Cavendish Laboratory in Cambridge report theoretical evidence that the neutron matter of the mantle may itself form a solid lattice—at pressures of about 10^{28} atmospheres which are easily accessible in neutron stars. The path by which they reach this conclusion is a novel departure

from more conventional techniques.

Their work is based on the quantum theory of corresponding states developed by J. de Boer (*Physica*, **14**, 139; 1948). This theory gives a method of comparing the properties of materials the constituents of which interact by potentials which are roughly similar in shape in the sense that they can be related to one another by a scaling of the radius and depth. Because the basic features of the nuclear force—a short range repulsion and longer range attraction—also characterize the interaction of such materials as ^3He , ^4He , H_2 , D_2 and Ne, Anderson and Palmer are able to estimate the solidification pressure of nuclear and neutron star matter by the appropriate scaling of the known solidification pressures of these substances. They obtain a solidification pressure of about 10^{28} atmospheres for both neutron and nuclear matter, a surprisingly low value.

The strongly empirical approach of Anderson and Palmer is clearly only an early step in the calculation of the properties of the neutron matter in neutron stars. Nevertheless, it shows that a solid mantle below the crust must be taken as a serious possibility.

different ranges. And, finally, the remanence seems to be contained in fine magnetic grains for which not even a theoretical self-reversal mechanism is known. Taken as a whole this evidence points pretty strongly to a true field reversal.

What conclusions have Dunn and his co-workers been able to draw from a palaeomagnetic study of the Tatoosh intrusion? The first is that the transition is reverse to normal and took place 14.7 ± 1.0 million years ago. More important, however, are the details of the reversal. At the start of the transition the intensity of the natural remanence dropped by an order of magnitude before any significant change at all took place in either declination or inclination. Towards the end of the intensity decrease the directions began to scatter a little but the main directional reversal took place later. During this stage the virtual geomagnetic poles (VGP) swung systematically along a great circle. At the end of the transition the intensity did not begin to increase until the direction had reached its fully normal state.

As Dunn *et al.* rightly point out, the variations in the intensity of the natural remanence are not necessarily proportional to variations in the intensity of the ancient geomagnetic field. Attempts to determine the absolute field intensities were complicated in this case by the fact that natural remanence and the artificially induced thermal remanences seemed not to be related linearly. Nevertheless, the field intensity values obtained confirmed the general form of the remanent intensity variations.

Unfortunately it was not possible to obtain a very accurate estimate for the time of the reversal because the cooling rates throughout the intrusive section were not very precisely known. Application of a theoretical cooling model to the intrusion suggested that a minimum resolution of only 1,000 years could be expected. But this seems to conflict with the experimental data. Motions of the VGP during the latter part of the transition were reminiscent of secular variations of VGP observed from archaeological data—that is, variations having periods less than 1,000 years. If these motions are correctly interpreted therefore, cooling would seem to have taken place faster than the theoretical model suggests. If it is assumed that the VGP movements were really attributable to secular variations having periodicities similar to those of the recent past the reversal time turns out to be 1,000 to 4,000 years for direction and about 10,000 years for intensity. But although these absolute figures are by no means certain, there can be no doubt that the reversal in direction was considerably shorter than the change in intensity.

ENZYMES

Siamese Twins

from our Molecular Biology Correspondent
A SPECIAL place in this bestiary of biochemistry belongs to twinned enzymes, which are generated by a cunningly aimed frame-shift mutation that blocks release of a completed polypeptide chain before initiation of the next one along the messenger. One such was achieved by Kohno and Yournio, who fused two enzymes of the histidine operon of *Salmonella*, histidinol dehydrogenase and imidazolylphosphate-glutamate aminotransferase. In wild type cells each of these enzymes is thought to exist as a dimer, with subunits of molecular weight around 40,000. Yournio, Kohno and Roth reported in *Nature* last year that in the Siamese-twin form the subunit has a molecular weight of some 85,000, the

dehydrogenase being on the N-terminal side of the aminotransferase. These composite chains were reported to associate to a quaternary structure which Rechler and Bruni (*J. Biol. Chem.*, **246**, 1806; 1971) found to be a dimer, suggesting that the subunit-interaction sites may also still be functional. Kohno and Yournio (*ibid.*, 2203) have now attempted to separate the two enzymes by trypsin cleavage, in the reasonable hope that the connecting peptide, not being presumably folded into the globular structure, would be especially labile.

Their efforts were only partly successful, because the aminotransferase is unfortunately very susceptible to attack by trypsin. The dehydrogenase activity, however, remains, and a subunit of the right size appears in detergent-acrylamide gel electrophoresis. The subunits in the

Molecular Defect of β Thalassaemia

THE linking of molecular biology to human medicine will be advanced by the finding reported by Nienhuis, Laycock and Anderson in next Wednesday's *Nature New Biology* that the molecular defect causing human β thalassaemia almost certainly resides in the amount or nucleotide sequence of the messenger RNA. β thalassaemia is a serious human haemolytic anaemia characterized by a reduction in the synthesis of β chains of haemoglobin. By taking rabbit globin messenger RNA and adding it to human cell-free protein synthesizing systems with thalassaemic and non-thalassaemic ribosomes, Anderson and his colleagues have shown that the thalassaemic and normal ribosomes behave identically, and thus the messenger RNA is presumably at fault.

Rabbit globin messenger RNA works in human reticulocyte systems, directing the synthesis of both α and β globin chains in large amounts. Species specificity problems did not arise, and indeed were not expected, for the globin sequences are very similar in rabbit and man. There is no significant difference in the proportion of α and β chains synthesized between thalassaemic and normal human ribosomes with added rabbit mRNA, demonstrating conclusively that thalassaemic ribosomes have the ability to recognize normal β chain mRNA, albeit from rabbits.

It has been shown previously that thalassaemia can be detected using cell-free systems in which only the polysomes are of thalassaemic origin, and the current work shows that the ribosomes are normal, so that only the mRNA can be defective. The Columbia group (Fuhr, Natta, Marks and Bank, *Nature*, **224**, 1305; 1969) have demon-

strated an accumulation of ribosomal subunits in thalassaemics, indicating a defect in initiation. Attention will now be focused on whether an alteration in sequence of the mRNA at the ribosomal binding site of the messenger for β chains can be detected in thalassaemia, which would provide the most consistent (though not the only) explanation for all the results.

There have been several other reports giving conclusive proof that the 9S RNA isolated from mammalian reticulocytes is the messenger for globin, a comforting thought for the many laboratories working in the field of mammalian protein synthesis. Proof of the existence of mRNA does not, however, solve the problems of translational control in mammalian systems, where a proliferation of factors implicated in initiation is occurring. Heywood (*Proc. US Nat. Acad. Sci.*, **67**, 1782; 1970) has put forward evidence, using a mixed myosin/haemoglobin synthesis system, that proteins exist which specifically recognize the mRNA and could act as a control mechanism. This fails to explain results such as those of Stavnezer and Huang (*Nature New Biology*, **230**, 172; 1971) who find that immunoglobulin light chain mRNA isolated from a mouse myeloma can be translated by a reticulocyte cell free system without the addition of specific factors. If immunoglobulin, why not myosin?

What with myeloma and thalassaemia, it is particularly encouraging that the many recent advances in isolation and translation of mammalian mRNA are finding an application in explaining so rapidly the molecular basis of human diseases.

active form are dimeric, but are associated with some peptide fragments, either from damaged dehydrogenase or from disintegrated aminotransferase. An interesting consideration is that the short length of chain tethering the C-terminal end of one enzyme to the N-terminus of the other does not prevent correct folding of either. It seems to follow that the termini are near the surface of the molecule, or else that some limited disorganization in these regions is permissible.

Somewhat related to this situation is a diverting experiment carried out by Taniuchi and Anfinsen (*ibid.*, 2291). As is now well known, their enzyme, staphylococcal nuclease, can be cleaved by trypsin between residues 48 and 49 to yield two fragments that can be recombined with regain of enzymatic activity. An interesting question then is what happens when such recombining fragments have overlapping ends. Following on their earlier experiments with short lengths of overlap, Taniuchi and Anfinsen have now examined the recombination of two long pieces, 1-126 and 49-149, which have an overlap of 78 common residues. Recombination is seen to occur (and can be followed by a change in tryptophan fluorescence), and activity returns. The same is true when a fragment with shorter overlap, 99-149, is used instead of 49-149. A part of the redundant segment, namely residues 99-110, is chewed away by trypsin in the reconstituted enzyme, with no loss in activity. With the larger fragment, two kinds of overlap are clearly possible, with redundancy at the terminal end of 1-126 or at the C-terminal end of 49-149. Digestion with trypsin and recovery of the undigested part, shows that four components remain: 1-48, 111-149, 1-126 and 49-149. In other words recombination of the overlapping fragments leads to an equilibrium mixture of the two types of complex, with either 49-110 of the C-terminal, or 49-126 of the N-terminal fragment, trailing harmlessly in the solvent. These results confirm the view that essentially all the sequence is needed for correct folding and activity, and indicate that the chain may be broken only at specific places if recombination is to occur. The cleavage and recombination moreover do not involve the interruption of the known α -helices, and the authors note that this is consistent with the notion that it is the latter which nucleate the refolding process.

The same issue of the *Journal of Biological Chemistry* contains the results of X-ray analysis by Cotton and his group (Arnone *et al.*, *ibid.*, 2302) of the complex of the nuclease with its diphosphate inhibitor. The constellation of residues in contact with the inhibitor is precisely defined, and Arnone *et al.* stress the absence of any

steric freedom in the positioning of the latter. (There is also the slightly startling feature of an interaction between the 5' phosphate of the inhibitor and a lysine from another enzyme molecule in the crystal.) As a demonstration of how effectively crystallography and protein chemistry can complement each other, this paper is linked to one by Chaiken and Anfinsen (*ibid.*, 2285), in which four of the residues in contact with the inhibitor have been replaced in synthetic fragments that are then recombined with the rest of the chain. With conservative substitutions of one residue for another of like charge, the fragment will in all cases bind, but no activity is generated. Thus all these residues, as well as some others, whose implication was established earlier, are indispensable for function, and it remains uncertain only whether they are required for catalysis, or for sterically precise interaction with the substrate or maintenance of the local chain conformation.

Measuring the Water-PTFE Contact Angle

In the forthcoming issue of *Nature Physical Science*, A. B. Ponter and A. P. Boyes of the University of New Brunswick report their recent work on the variation of the contact angle of water drops on a low energy surface such as polytetrafluoroethylene (PTFE) with temperature and pressure. The quantitative study of contact and wetting of surfaces by liquids is difficult because of the considerable variations caused when even small traces of impurities are present on the surfaces. Although in some cases the nature and purity of surfaces can be studied and tested by very sensitive techniques such as grazing incidence electron diffraction, it is often extremely difficult to obtain useful indications of the degree and nature of impurity traces of monomolecular dimensions or less. Nevertheless the behaviour of liquids on solid surfaces is clearly a matter of great importance in everyday life and in industry. The condensation of steam, for example, in condensers in industrial power plants is an important process which is most efficient when the condensed water forms drops which hinder further contact of the water vapour with the cool surface as little as possible. Organic layers deposited on condenser surfaces can be used to promote such dropwise condensation.

It is therefore clearly desirable to understand the basic features of the contacting of solids by liquids. The experimental observations of Ponter and Boyes on the contact angle of water on PTFE provide particularly useful new data obtained under con-

EARTH'S ATMOSPHERE

Natural CO Sources?

from our Geomagnetism Correspondent

It is fortunate that the lifetime of carbon monoxide in the atmosphere is short, for the principal source of this gas is the burning of fossil fuels by man. During the past few years, however, it has become clear that there are also significant natural sources. Measurements in the Atlantic and Pacific Oceans, for example, by Swinnerton and his colleagues at the US Naval Research Laboratory in Washington DC, have shown that the oceans contribute at least 5 per cent of the amount of carbon monoxide generated by the burning of fuel. The oceans thus seem to be the largest natural source, though knowledge of the various sources and sinks of carbon monoxide within the geochemical cycle is far from complete. At present the field is wide open to the discovery of other sources; and an overall assessment of the fate of

ditions of condensation, that is with the water at its boiling point in an atmosphere of water vapour only. Their experiments were carried out over a range of pressures from 17 to 759 torr corresponding to boiling points of 21 to 100° C and their results show that the contact angle of the water drops is almost constant at 105° over these ranges of temperature and pressure.

This finding is similar to several earlier conclusions of the constancy of the contact angle of water in air over a 60 to 70° C temperature range, for example by Adam and Elliott (*J. Chem. Soc.*, 2206; 1962) for water droplets on solid hydrocarbons, by Phillips and Riddiford (*Nature*, **205**, 1005; 1965) for water on a siliconed glass surface, and by Neumann (*Akh. Deut. Akad. Wiss. Berlin Kl. Chem. Geol. Biol.*, 811; 1966) and Phillips and Riddiford (*J. Colloid Interface Sci.*, **22**, 149; 1966) for water on a teflon surface from room temperature to 60° in air saturated with water vapour at atmospheric pressure. Several workers, however, have found in favour of a temperature dependence in other cases and both positive and negative temperature coefficients have been suggested.

Ponter and Boyes further point out that their observations lead to the conclusion that $\left[\frac{\delta}{\delta T} \left(\frac{W_{SL}}{\gamma_L} \right) \right]_P$ must be negligible, like $\left[\frac{\delta}{\delta P} \left(\frac{W_{SL}}{\gamma_L} \right) \right]_T$; W_{SL} is the work of adhesion to the film-free solid, and γ_L is the free surface energy of the liquid.

atmospheric carbon monoxide remains to be carried out.

That there are other sources besides the oceans is the chief conclusion to emerge from the latest work of Swinnerton *et al.* (*Science*, **172**, 943; 1971). These workers have now found that in various samples of rainwater there is a high degree of supersaturation of carbon monoxide relative to the partial pressure of carbon monoxide in the atmosphere. The samples were from three widely separated and very different environments in the United States and the Pacific Ocean. The first set of samples was in Washington DC, in the heart of civilization where atmospheric pollution can be considered significant; the set was taken aboard a ship in the Pacific with the collector well forward of the funnels and while the ship was heading into the wind; the third set was from two different sites in Hawaii—in Hilo, the largest community on Hawaii, and in the interior of the island upwind of active volcano sites. All samples were then analysed immediately for both carbon monoxide and methane with the exception of those from the Hawaiian interior which were analysed within two hours of collection. At all sites air samples were also taken and analysed similarly.

As might be expected the carbon monoxide concentrations in the air samples were indicative of the environments. Thus in Washington they were high and very variable, in the Pacific they were much more constant and low (on average about fifteen times lower than in Washington), in the Hawaiian interior they were slightly higher than in the Pacific, and in Hilo concentrations were about twice as high as those in the Pacific, in accordance with a small town environment. In the Pacific, where pollution can be considered negligible, the absolute concentrations of carbon monoxide were about 0.10 p.p.m. of air. At all sites, however, the rainwater was supersaturated with carbon monoxide with respect to the atmospheric concentration, up to factors of 200. Even more surprisingly, the supersaturation was highest in regions where pollution was least—in the Hawaiian interior and over the Pacific. For methane, however, the story was completely different. In all cases the concentration of methane in rainwater was in rough equilibrium with the partial pressure of methane in the atmosphere.

Why is rainwater supersaturated with carbon monoxide? A clue may come from the observed variations of supersaturation with height. In the Hawaiian interior at altitudes of 2,000 to 5,000 feet the degree of supersaturation is significantly higher than in Hilo which is roughly at sea level. This is in accordance with the expectation that rain-

water will lose supersaturation as it falls through the atmosphere; but by the same token it suggests that the source of the carbon monoxide is in the region where the rain is formed—that is, in the clouds.

Swinnerton and his colleagues then go on to suggest two possible mechanisms for the formation of excess carbon monoxide. The first is a possible photochemical oxidation of organic matter. It is now known that rainwater contains low concentrations of organic matter; and Wilson *et al.* (*Science*, **168**, 1577; 1970) recently showed that photochemical oxidation of organic matter leads to the produc-

tion of carbon monoxide in seawater. The same process could take place in rainwater.

The other possibility discussed is electric discharge in the clouds leading to a slight dissociation of carbon dioxide. Laboratory studies have already shown that such a process is possible, although Swinnerton *et al.* consider that it would not be able to account fully for the observed atmospheric concentrations of carbon monoxide. Both these mechanisms are, of course, speculative. But what does seem certain is that by one means or another the atmosphere itself is another natural source of carbon monoxide.

The Migration of Hawaiian Volcanism

THE Hawaiian Island Chain has long been a source of fascination to geologists, from the time that Dana visited it as part of the US Exploring Expedition (1838–1842) to the more recent use of Hawaiian volcanic lavas for determining the outline of the geomagnetic polarity-time scale. It was Dana, in fact, who first noted that the active volcanoes at the extreme south-east of the chain give way to extinct volcanoes which became progressively more eroded towards the north-west. He suggested, as a result, that the centre of eruption had migrated to the south-east—a view which is still held by geologists today notwithstanding the advent of the new global tectonics.

In one sense, of course, the very existence of the Hawaiian Chain and others like it in the Pacific is an anomaly as far as global tectonics is concerned. The principal sources of volcanic activity lie along the worldwide ridge-trench system; but the Pacific island and seamount chains lie on large, nearly straight, aseismic ridges which strike roughly at right angles to the East Pacific Rise but occur a long way from it. How then, if at all, do such chains fit into the pattern of seafloor spreading and plate tectonics? As Tuzo Wilson (*Nature*, **197**, 536; 1963) pointed out, the facts are not necessarily irreconcilable. He visualized a spreading Pacific Ocean crust moving over a deep localized magma source. In such a scheme a volcano on the crust would ultimately become dissociated and get carried away from its source in a north-westerly direction, and a new volcano would arise in its place. This does, of course, beg the question of the nature of the magma source; but given that the source exists its behaviour is entirely explicable in terms of seafloor spreading.

Wilson's qualitative view is now widely accepted. In next Monday's

Nature Physical Science, however, McDougall takes Wilson's model considerably further by putting it on a more quantitative basis. There is now so much radiometric age data available from the Hawaiian Chain that McDougall has been able to make a pretty good estimate of the migration rate of the Hawaiian centre of volcanism and thus compare it with previously determined rates of spreading of the lithosphere away from the East Pacific Rise. Thus he determines the migration rate from the age of cessation of eruption of the tholeiitic magmas from each of the volcanoes now extinct in the Chain and the distance from the currently active volcano on Hawaii itself. The average figure he then comes up with is 15.2 ± 1.4 cm per year. The magnitude of the standard deviation here shows that during at least the past 16 million years the migration rate has remained remarkably constant, which suggests, in turn, uniformity in the processes involved in the formation of the chain.

In comparison, the rate of seafloor spreading away from the East Pacific Rise in a roughly north-east direction is about 6 cm per year, or somewhat less than half of the migration rate of the volcanic centre. This suggests that, by the seafloor spreading hypothesis, the return flow of material in the asthenosphere towards the East Pacific Rise is taking place with roughly the same velocity as the flow of the lithosphere in the opposite direction—and that the source of Hawaiian volcanism lies right in that part of the upper mantle (the asthenosphere) which contains the return flow. This accords well with theory. The asthenosphere, which is thought to correspond roughly with the low velocity seismic zone, is commonly supposed to be a layer of partial melting in the mantle which would thus serve as an obvious source of magmatism.

TRANSPLANTATION ANTIGENS

What are They There For?

from a Correspondent

THE International Union of Immunological Societies sponsored a meeting in Rovinj (Yugoslavia) from May 16 to 21 on the biological significance of transplantation antigens, the object being to integrate the young generation with the jet-set and fill the painful gap between the discussion-less congress and the small high-level discussion meeting ("workshop"). Everybody was happy with the outcome because the effort approached closely to its goal and the shortcomings (only two) are easily pinpointed.

The first problem did not affect the proceedings themselves, thanks to the organizers; there were difficulties in accumulating sufficient funds to run the meeting and the IUIS itself seems to have had difficulty in providing practical help. Everybody believes this is an important kind of meeting and it is a pity to discourage a series by a threat of financial problems to anybody gallant enough to undertake the organization of a sequel.

The only other defect can be attributed to the speakers, and highlights a problem that is widespread at scientific meetings. The participants came from twenty-two different countries and were all familiar with the international language of science, through reading it but not by listening to it. In view of this fact, nearly all lectures covered too much, were given too quickly, lacked explanation of the aim, included unreadable slides or suffered from some combination of these things. The slides were especially bad; many were photographs of tables from recent publications, in some cases having twenty rows of figures in ten columns. It might help in the future if speakers gathered a day earlier for a brain-washing on these points by the committee and a censorship session on slides.

A morning devoted to possible physiological roles of histocompatibility antigens outside the context of transplantation resulted in a list of ten possibilities and an excellent discussion led by Professor M. Simonsen (University of Copenhagen). No conclusions were reached, of course, and no majority favoured any particular item.

Whereas the human HL-A people, for example Dr E. Thorsby (Blood Bank, Oslo), would like the mouse H-2 people to see the immunogenetics of H-2 through HL-A eyes, some immunologists, for example Dr D. A. L. Davies (Searle Research Laboratories, High Wycombe), would like to see a converse trend; unlike the HL-A matched sibling situation, "full house" matched unrelated individuals always

give a mixed lymphocyte reaction and, according to Professor J. J. van Rood (University of Leyden), do not accept each other's skin grafts for longer than unmatched recipients. What is missing?

Association of diseases, leukaemia especially, with HL-A phenotype is clear, but it was astonishing how different speakers' data diverged in statistical significance. The effect is, hopefully, connected with the association of immunological responsiveness and histocompatibility genotype, on which data from mouse studies are rapidly accumulating.

The roles of B and T cells (bone-marrow derived and thymus dependent respectively) and their interaction in immune responses are rapidly clarifying. Preformed immunoglobulin is accepted as the B cell recognition site but the general feeling of the meeting was that the T cell receptor remains unidentified. Although Professor Simonsen sugges-

ted that this might not be related to immunoglobulin (IgX) but that indeed it might be histocompatibility antigen itself, Professor H. Ramseier (Institute for Immunology, Hoffman-La Roche, Basle) and Dr Davies thought this less likely because of the ability of anti-receptor site antibodies to immunosuppress T cell activities.

Donor specific immunosuppression was discussed at length (no mention of ALS for a change!); three mechanisms seem distinguishable—tolerance (antigen-induced), enhancement (antibody-induced) and recognition site interaction (antibody-induced). The distinction between the first two is no longer as sharp as it once seemed to be. The distinction between the last two is clear because the antibodies are absorbed only by donor or host cells respectively. No new concepts emerged; the most debated subject was anti-recognition site antibody put forward by Professor Ramseier.

Mechanism of Genetic Polarity

IN the next issue of *Nature New Biology*, Kuwano, Schlessinger and Morse add their voices to the current dispute about the mechanism of genetic polarity in *Escherichia coli*. When a nonsense codon, either UAA, UAG or UGA, arises by mutation in a gene only a stunted protein is made when the gene's messenger RNA is translated, for the cell's translation machinery disengages from a messenger when it encounters one of these chain termination codons, the full stops of the genetic language. More often than not, of course, the stunted polypeptide chain specified by a gene with a nonsense mutation is completely inactive—the gene is killed—but this class of mutations can have an even more devastating effect. When a nonsense mutation occurs in the first gene of a multigenic messenger RNA, the translation of the subsequent genes may be greatly reduced, even though they themselves do not carry any mutation. The molecular mechanism of this pleiotropic effect of nonsense mutations—called polarity—is currently very much in dispute.

There are three obvious possible mechanisms; first, a polar nonsense mutation might prevent the copying into messenger RNA of genetic sequences following the nonsense codon if the process of transcription is closely coupled to the translation of messenger RNA; second, a polar mutation might, by causing the ribosomes to fall off a messenger, leave the messenger accessible to nucleases which are usually unable to attack because ribosomes are in the way; finally, it might be necessary to translate one gene in order to destroy some secondary structure which

masks the start signals of subsequent genes.

These alternatives are clearly not mutually exclusive and it seems that there may well be no universal mechanism of polarity. Polarity in the RNA phages, for example, is apparently based on the third of these alternatives, but arguments about polarity in the tryptophan operon of *E. coli* centre round the first two mechanisms. Kuwano and his colleagues favour the idea that polar nonsense mutations, by freeing *trp* operon messenger of ribosomes, render the RNA accessible to a previously undetected endonuclease which divides the molecule into fragments which can then be further degraded.

Their evidence is indirect; they have shown that bacteria carrying a mutation called *SuA*, which relieves polarity in the tryptophan operon, have less endonuclease than bacteria lacking the *SuA* mutation. The *SuA* mutation, they suggest, inactivates the endonuclease responsible for chopping the tryptophan messenger and because it survives polarity is abolished. It is interesting that Summers recently reported in *Nature New Biology* (230, 208; 1971) that when an amber mutant T7 phage infects *E. coli* carrying the *SuA* mutation, more T7 messenger from the mutated gene survives than when bacteria without the *SuA* mutation are infected. In short, it seems that in some cases polar mutations do render messengers more accessible than usual to nucleases by depleting the molecules of ribosomes and so reduce the extent to which genes, beyond that carrying the polar mutation, are expressed.

Rewards for Inventors

P. M. B. WALKER

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Professor Walker describes two contrasting personal experiences as an inventor and suggests that inventors should be encouraged to participate much more fully during the period of translation of an idea into a commercial product.

NOWADAYS universities and research institutions are expected to provide a greater contribution to the welfare of the society which supports them. Many of their implied shortcomings in this respect are based on an ignorance of the nature of fundamental research, but there remains a wide area, principally concerned with the commercial exploitation of new ideas and technologies, where much could still be done. Universities in Britain are responding by setting up centres for industrial liaison and the old attitudes of some academics towards commerce and industry are disappearing¹, although an over-zealous acceptance of industrial guidance in university affairs is probably now recognized to be equally disastrous. The Science Research Council has followed the same trend by allocating both research grants and research studentships to joint university industry projects.

In spite of these changes in the climate of opinion, the position of the inventor, particularly in government sponsored research laboratories, is anomalous and unsatisfactory both from the national and the personal viewpoint. Inventions arise in industry, in government sponsored research laboratories (including both laboratories supported directly by government departments and those supported by the research councils) and in universities. Obviously industrial research has its own problems but industry is in business to exploit inventions, whereas most government research laboratories and universities are not. Indeed, the aims of university and research council supported research should be to ensure that a high proportion of really productive and revolutionary new ideas originate in these institutions.

My own experience in this field has chiefly been in research council and university employment although I worked in industry for several years, and have served as an industrial consultant more recently. I shall discuss the position of inventors from two viewpoints: first, how we can encourage

the transformation of a new idea into a saleable invention, and second the kind of cooperation which an industrial firm can expect and encourage from a research worker.

Doctrine of Total Employment

The most basic problem is that of direct monetary reward to inventors. The most powerful argument used to justify the failure to reward inventors is the doctrine that the research worker is anyway employed to invent and so there is no reason why he should be paid again for a normal part of his duties. The argument is used chiefly in government sponsored and industrial research and is not heard much now in universities. In industry the effect of the doctrine is perhaps less pernicious both nationally, because the inventions will probably be exploited anyway, and personally, because greater salaries flexibility and the possibility of alternative employment may combine to satisfy the inventor.

Although I do not intend to consider the position of inventors in industry in any detail, two points are worth making. First, the position of inventors in British industry is, in law, considerably less favourable than in many other countries². Second, certain US corporations find it economically justifiable to pay substantial rewards to inventors among their staffs. Westinghouse Electric International, for example, have a high reputation for technical innovation and pay as much as \$15,000 for shop floor improvements alone.

I believe that in non-industrial research there are many anomalies stemming from confusion about the nature of inventions. The pattern of scientific research, as generally understood, is the testing of new ideas, the discovery of improved explanations for natural phenomena and, sometimes, the development of new techniques and new substances. No research council or, presumably, government department will prevent its staff from accepting prestigious prizes even when given for new and patentable techniques; neither do they attempt to recover any of the royalties paid to the authors of reviews or the editors of learned books. All these emoluments are for activities very closely connected with what is generally considered to be the scientific research for which the individual is paid. It is only if an idea turns out to be patentable and can be exploited by a commercial firm other than a publisher that the doctrine is invoked. The result is that potential inventors are deterred from looking at the wider application of their ideas and make no effort to see if society can gain some immediate benefit from them. The original idea is not an invention

either in common experience or in law—the act of invention is the realization that a development of that idea could have a practical use. Most research scientists are paid and encouraged only to provide the first kind of synthesis.

Publishing is considered more praiseworthy because new results are made generally available. Patenting implies exclusive rights, although details of the invention may be fully published later, and it is therefore often felt to be inconsistent with scientific propriety. But in practice industry will rarely risk money for further development unless it is protected from the possibility that rivals will pirate the finished and developed designs. The National Research Development Corporation (NRDC) was set up in 1949 to relieve the scientist of the burden of dealing with what were then thought to be rather disreputable matters, but in so doing it may also divorce him from his invention. It is therefore worth considering how effective the corporation has been in promoting the more rapid development of inventions.

Role of NRDC

The NRDC has two principal roles: on the one hand it patents inventions arising from “public research” and then licenses them to industry for development and marketing, and on the other it both finances the development of inventions in universities and, in collaboration with industry, those like the hovercraft and carbon fibres, which seem to require further investment before they can be made commercially viable and which industry on its own does not consider to be a reasonable commercial risk. The two sides of this work are often inter-related, but I will concentrate on the patenting and licensing aspect of these activities.

Recently most of the patent rights assigned to the NRDC have come about equally from universities and from more directly government supported research². About 200 patents arise from each sector every year. There are many and obvious reasons why inventions are sometimes unsuccessful, and it may be that the total of just less than 600 revenue earning inventions in the 21 years up to 1970 represents a reasonable success rate. As I have already implied, however, there is at least the possibility that the substitution of a corporation for the direct and educative interplay between inventor and industry may eliminate something essential for the successful exploitation of many inventions. The problem of analysing the nature of this delicate relationship between inventor and industry is that no single case is typical, but I will consider the problem from my own experiences because they illustrate rather well several aspects of this relationship and provide at least one insight into the role of the NRDC.

About 18 years ago I was a junior member of the staff of a Medical Research Council unit and I was trying to measure the optical density of ultraviolet photomicrographs of living cells. I had constructed a primitive double-beam microdensitometer for my own use⁴ and I could see how a more sophisticated design might be used for measuring the larger spectrographic and X-ray plates with which my colleagues were working. The result was an instrument⁵ with, I believe, a certain elegance in the disposition of its parts and a wide range of applications.

The completed recording microdensitometer attracted the attention of a very small Gateshead firm of instrument manufacturers, Joyce, Loeb and Co. Ltd, and they licensed the instrument from the NRDC to whom, as a research council employee, I had had to assign my rights. Over the years Joyce, Loeb have grown and made many detailed improvements to the instrument, but it is still recognizably the same. It has been one of the few British scientific instruments found in laboratories all over the world, although it is now being superseded for some applications by much faster instruments recording directly in a computer compatible manner (for example, ‘Scan-Dig’ manufactured by Technical Operations Inc.).

After NRDC assumed responsibility for the invention I

had very little to do with the subsequent development of the microdensitometer particularly in the critical early stages of its manufacture. The manufacturers expected more information and expertise from the NRDC for the royalties they were paying, but as I usually design components as I make them and because Joyce, Loeb were unfamiliar with some of the basic optical principles which often dictated the design solutions, drawings were sparse and progress slow. Joyce, Loeb were also inhibited from asking too much of the inventor's time, as they were not allowed to pay consultants fees. It is therefore understandable that my relationships with the manufacturers were strained, although they improved considerably later.

Recognizing Difficulties

Quite apart from the lack of royalties, which are an important consideration in our society, no inventor likes to see his invention disappear into the files of an anonymous corporation, however efficient. When, as in other cases, they seem to lie there indefinitely, the inventor will lose interest and begin to doubt if others could ever be as keen as he would be in canvassing his ideas.

These difficulties have to some extent been recognized recently; the Medical Research Council now allows its employees, like those of a university, to accept paid consultancies and it also operates a scheme whereby a tax-free payment of up to about 5% of the total royalties received by the NRDC may be paid to inventors. It also has a number of collaborative agreements with universities and individual pharmaceutical firms which seem to work well, and are particularly important in situations in which commercial facilities can provide large quantities of new substances for evaluation. Other research councils, including the Science Research Council, now have similar arrangements, but they all still believe that the public interest is best served by not allowing individual research workers to make direct arrangements with industry in respect of inventions arising from research council supported work.

The presence of the NRDC as a kind of middle man in the relationship between inventor and industry may, therefore, be a positive deterrent in some cases to the exploitation of inventions. There is no doubt that it has great expertise in protecting them and the inventor, and it may also have a considerable role in financing their commercial development, but psychologically its presence probably hinders the second creative step of seeing a new idea as an invention. This role of the NRDC may also neglect the crucial nature of the relationship between the scientist and the managers and engineers who seek to exploit his ideas.

Participation of the Inventor

The importance of this relationship can be highlighted by my contrasting and more recent experience with a new kind of analytical centrifuge. During normal research work my colleagues and I make extensive use of a conventional analytical centrifuge for characterizing the various DNA fractions which we isolate as a matter of routine^{6,7}. Without an expensive modification these instruments only provide a photographic record which then has to be measured on the Joyce, Loeb microdensitometer. It occurred to me that a much simpler direct recording instrument could be made if each separate element along the major axis of the centrifuge cell could be separately illuminated and the absorbance of these elements directly measured in relation to identical elements in a blank cell.

I discussed this plan with Measuring and Scientific Instruments Ltd, the British manufacturers of high speed centrifuges, and in due course they agreed to finance a small research project to test its feasibility. There followed a most interesting period which has culminated recently in the completed ‘Centriscan 75’. The period was stimulating and productive for

two important reasons. First, the instrument was directly related to my principal research interests; the provision of a new centrifuge of this type would materially help in our work and the presence in the department of an instrument technician meant that the centrifuge development could occur without my continuous involvement. Second, and this was most important, arrangements were made for the "inventor" to participate in and discuss most of the decisions and problems which arose during the translation of the idea into a machine. Regular progress meetings were attended by managers, development engineers and physicists. From time to time new problems could be referred back to the laboratory and in this way rapid progress was made in an atmosphere in which free and critical discussion was welcomed. It was obvious that the education of the academic scientist in the problems of management and production was a significant factor in the whole process.

The contrast between my two examples is self evident. But to what extent are the differences caused by the restrictions imposed by research council employment and university employment, and how much are they due to the greater maturity and experience of the participants in the centrifuge programme? Undoubtedly experience has played a part; it certainly leads me to believe that cooperation with industry without some financial obligations, without the project having some relevance to the basic research interests of the academic scientist and without active participation in the decisions made during the development of the project, may often lead to mutual dissatisfaction.

Obstacle to Liaison

It seems also that whatever the formal structure allowed by the rules governing employment by research councils or government departments, the mere presence of a buffer cor-

poration must be an obstacle to the kind of close liaison that occurred during the centrifuge project. One has only to think of the possible disputes about ownership of rights in the ideas originating in the course of development of such an instrument to understand the difficulties.

Universities are now increasingly taking on the responsibilities of protecting and advising inventors and consultants among their staffs by setting up centres for industrial liaison. The benefits of such advice, even if it includes royalty sharing with the local centre, are seen to return to the local institution and are under academic control. If the development of inventions was viewed in the same light as scientific publication—in which the inventor can retain a direct interest—then perhaps research councils could also manage these limited functions of protecting, licensing and advising inventors for themselves. Even research institutions directly financed by the government might be allowed this much self help. Indeed, it could well be thought of as further progress towards standing on one's own feet.

There are difficulties, of course, but no one expects every scientist to become an inventor overnight; the problem is to create the right conditions for the minority who have this kind of talent and inclination.

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Biosynthesis of Antibodies

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The aim of this short review is to draw together current ideas about antibody synthesis.

THERE are a number of hard facts, many uncertainties and no shortage of hypotheses about antibody synthesis. I have attempted to fit the facts into a generalized scheme and have been selective in the choice of theoretical ideas with which to fill in the remaining gaps. Many of the data on which I have drawn have been discussed in more detailed review¹⁻¹⁰; only some more recent papers are independently referenced.

All vertebrates from hagfish to man are capable of synthesizing specific antibodies in response to an extensive variety of antigens. To induce antibody production, it is usually necessary, but by no means sufficient, that the antigen be "non-self", that is, foreign to the organism. Presentations of

antigen, usually macromolecular, capable of eliciting antibody are conveniently referred to as immunogenic substances. Properties which delineate an immunogen have been reviewed already^{11,12}. Antibodies belong to a class of molecules collectively defined as immunoglobulins (Ig), which consist of two types of polypeptide chains, heavy (H) and light (L), in symmetrical four-chain units which exist either singly (IgG) or in multimeric form (IgA, IgM).

Cells producing Ig

Lymphoid cells of various types synthesize Ig, and the extent of production, heterogeneity of the product and dependence of production on antigen vary among the cell types. A simplified summary is given in Fig. 1. Cells classified as small lymphocytes express receptor antibodies which are plasma membrane components. There are two major classes of receptor-bearing small lymphocytes, which for the purposes of this article I will refer to by the terms antibody-secreting cell precursor and

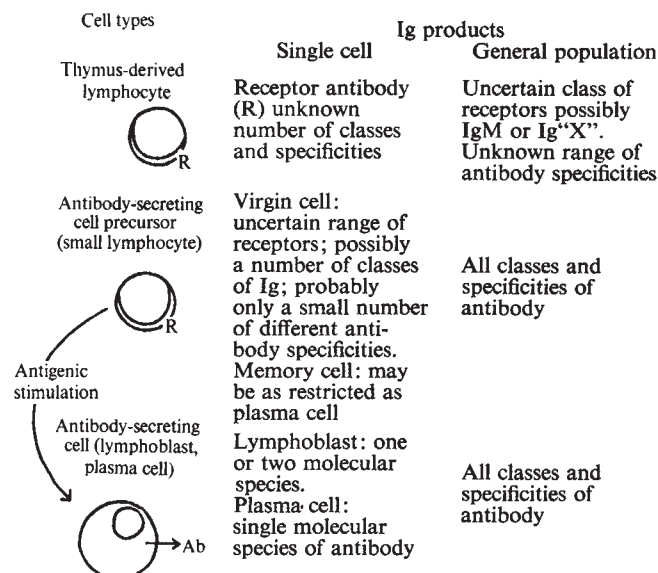


Fig. 1 Lymphoid cell types and their immunoglobulin products. The product restrictions of a single cell are listed in the first column and the range of products of the whole population of cells in the second. Precursors of antibody-secreting cells are divided into two classes: virgin cells, which have not yet seen antigen; and memory cells, which have been selected by antigen contact. This division may be too simple.

thymus-derived cells^{6,7}. Receptor antibody production by either class of lymphocytes is assumed to be initially a constitutive process in the sense that it occurs without the intervention of antigen. This does not rule out a possible increase in surface density of receptors after antigen contact.

The first class of receptor-bearing lymphocytes consists of apparently bone marrow derived (thymus-independent) cells which, when stimulated by antigen, give rise to clones of antibody-secreting cells. The ultimate cells in this clonal proliferation are fully differentiated plasma cells which synthesize and secrete about 2,000 Ig molecules per second per cell.

Thymus-derived receptor-bearing lymphocytes function primarily in cell-mediated immunity but also play a role in antigenic stimulation of bone marrow derived cells^{6,7}. There is much scope for molecular studies of these functions.

Genetic Control

The two basic types of Ig polypeptide chains, L and H, occur in various polymorphic forms: two types of L chain (κ , λ) and various classes of H chain (α , γ , μ , ϵ , δ) each divided into several subclasses. Allelic variants (allotypes) are known at the loci controlling these polymorphisms; their behaviour is strictly Mendelian¹³. Amino-acid sequences of H and L chains produced a genetic paradox which has given birth to a novel concept of two genes—one polypeptide chain^{14,15}. The N-terminal sequences of between 105 and 120 residues of either H or L chains have been found to be unique for each chain studied, irrespective of the remaining C-terminal sequence similarities (with the exception of mouse λ chains¹⁶). Consequently, it has been proposed that each Ig chain is the product of a unique V gene coding for the variable N-terminal sequence and one of the C genes encoding the constant class specific sequences. Antibody specificity depends on the V gene sequences. Current sequence data^{17,18} (discussed later) strongly suggest that a single pool of V_H genes is shared by all C_H genes but that the C_1 and C_2 genes have exclusive V_1 and V_2 gene pools.

Hypotheses about the genetics of antibody diversity divide on the question of the size of the V gene pools. Clearly in each mature individual the total V gene pool is large. Germ-line hypotheses maintain that the whole available V gene complement is present in each cell and is transmitted as a heritable

linkage group^{15,55}. Alternative proposals consider that there are only small V gene pools in each cell and predict hypermutability-hyperselection mechanisms operating at a somatic level to generate V gene diversity; each cell would carry different V gene pools and the sum of these for all immunocompetent cells give the large V gene potential of the individual³.

Gene Expression

The Ig phenotype differs among the various cell types (Fig. 1). I will discuss Ig production by cells at various levels of differentiation and it is convenient to start with the more differentiated secreted cell because most biosynthetic studies have been made on such cells. The diversity of Ig expressed by less differentiated cells is controversial. Receptors on thymus-derived cells are enigmatic. In the bone marrow derived cell line, I have taken the view that a virgin lymphocyte (before antigen contact) has the potential to express several different receptors and I have suggested a genetic basis for limiting this multipotentiality.

First I shall consider transcription-translation. The major features of constitutive immunoglobulin biosynthesis are now apparent and various aspects have been reviewed^{5,8-10}. In spite of the unique primary structure of Ig chains no novel mechanisms of RNA or protein biosynthesis can be implicated. The fully differentiated plasma cell synthesizes only single variants of H chain and/or of L chain. This implies selection of information from two V genes and two C genes excluding all other polymorphic or allotypic possibilities. The available evidence points to the integration of V and C gene information for a single chain at the DNA level. L and H chains are synthesized on separate polyribosomes as complete polypeptide chains with one N-terminal initiation point. This implies mRNA molecules encoding complete L and H chains respectively. Searches for putative biosynthetic intermediates corresponding to separate V and C region mRNA molecules or polypeptide chains have proved negative with one recent exception¹⁹ which remains unexplained, but unconvincing. The synthesis of separate V and C polypeptides would be difficult to reconcile with recent experiments demonstrating the cell-free biosynthesis of complete L and H chains; when the active polyribosomes were freed from their accompanying membrane complete L and H chains were still produced though they were no longer assembled into four chain Ig molecules²⁰.

Single mRNA molecules for L or H chains could result from linkage of separate V and C messages as well as from transcription of integrated VC genes. Simply the failure to detect any defects of mRNA linkage in innumerable generations of transplantable mouse plasmacytomas suggests a more stable form of encoding VC linkage. The existence of rare mutant H chains (H chain disease) which show extensive deletion of V and C sequences through the junction is most easily explained by the pre-existence of integrated VC genes^{21,22}.

After translation completed L and H chains first interact non-covalently and then the appropriate interchain disulphide bonds are formed. Short carbohydrate chains are added at specific points along the Ig chains, usually on H chains. For IgA, dimerization of the four-chain structure is common while for mammalian IgM the normal form in serum is a pentamer of four-chain structures, stabilized by disulphide bonds. All these processes precede secretion.

The secretion of Ig is predestined in a similar fashion to secretion of pancreatic extracellular proteins²³. Polyribosomes translating L and H chain mRNAs are arrayed on the endoplasmic reticulum (how this segregation of polysomes synthesizing export proteins arises remains an intriguing question). Nascent L and H chains grow through the cell membrane into the cisternae; this has been shown by the vectorial release of nascent chains prematurely terminated with radioactive puromycin²⁴. Completed chains are naturally released into the cisternae^{20,25}. In this discrete environment, the chains interact

to form four-chain structures. In a cell-free system, as noted earlier, the presence of the microenvironment provided by the membranes is important for assembly²⁰.

Non-covalent interaction between pairs of chains, L with H or H with H, must precede any covalent interchain disulphide bond formation. Because there is a usually small pool of free L chains in the cisternae, serving as intermediates in Ig assembly, newly completed H chains should rapidly interact with L chains. Indeed, interaction between free L chains and nascent H chains has been demonstrated^{26,27}. Dimerization of nearly completed nascent H chains is also possible²⁷.

In certain Ig molecules the four-chain structure is maintained solely by non-covalent interactions²⁸. More usually, interchain disulphide bonds have evolved. Although the order of non-covalent chain interaction is difficult to ascertain, the order of covalent linkage (L-H or H-H) can be defined by isolating covalently linked intermediates. A general pattern to the order of disulphide bond formation is discernible. The simple rule seems to be that the more stable type of interchain disulphide bond forms before the more labile type; stable and labile refer here to ease of reduction. Reducing conditions would be expected at the site of protein synthesis so the order of interchain disulphide bond formation could be envisaged topographically as a function of the removal of non-covalently assembled molecules from the reducing environment. For a number of murine G-myeloma proteins, for which the H-H disulphide link has been shown to be more stable than the L-H link, the major covalent intermediate in assembly has been found to be H chain dimer^{5,10}. For a murine M-myeloma protein (104E)²⁹ and for rabbit IgG³⁰ the L-H link is the more stable and here the major intermediate in biosynthetic assembly is the half molecule LH.

Carbohydrate Chains

Four-chain Ig molecules are transported through smooth membrane compartments for secretion by way of the Golgi apparatus. During this passage from the site of synthesis to the plasma membrane, short carbohydrate chains grow at specific sites on the Ig chains (usually on H chains). Currently available evidence suggests that the addition of the first sugar residue is on nascent chains⁸, though indirect evidence suggests that addition shortly after chain completion is likely in some cases³¹⁻³³. Subsequently the stepwise addition of mono-saccharides^{8,34} is catalysed by glycosyl transferases present in rough and smooth membranes³⁵.

All types of Ig reach the plasma membrane as four-chain structures. IgG molecules are secreted as such. IgA is found extracellularly both as monomer and dimer while IgM normally exists in serum as a covalently assembled pentamer of the basic four-chain structure. Superassembly of the four-chain monomer takes place at, or immediately before, the time of secretion of IgA and IgM. Radioactive labelling studies *in vitro*, using murine M-myeloma tumour 104E, showed that only the monomer "IgMs" could be detected inside the cell and only pentameric IgM outside³⁶. A mechanism for superassembly is not currently available. Only weak non-covalent forces act between IgM subunits, and reassociation between isolated IgMs is dependent on concentration. On native IgMs the sulphhydryl groups, which eventually form inter-IgM links, are apparently blocked; this suggests that an enzyme (for example, the microsomal enzyme which catalyses disulphide interchange in proteins³⁷) may be required for superassembly. Known defects in superassembly may cast some light on the process³⁸ (see other references quoted in ref. 36).

Regulation of Gene Expression

There is still much to be learned about the control of Ig synthesis at all levels. Information so far has come mostly from two systems: neoplastic plasmacytomas (myeloma tumours) are representative of more mature cells in an immune response; cultured human lymphoid cell lines provide a model system of

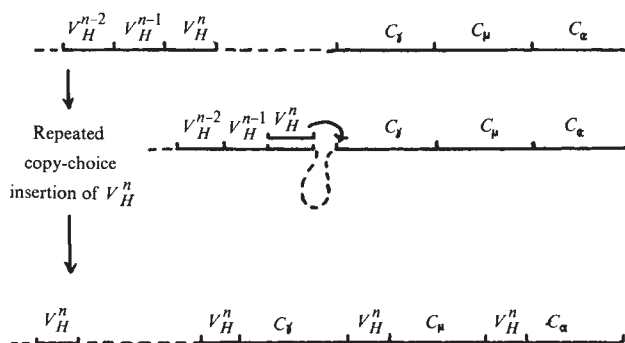


Fig. 2 Hypothetical scheme for the copy-choice integration of a single V_H gene with each of the C_H genes on the same chromosome. Only three C_H loci are shown for simplicity.

blast-like cells morphologically intermediate between precursor cells and plasma cells.

Human lymphoid cells have been cultured from many individuals exhibiting a range of known syndromes or no apparent defect. Most cultured cells secrete small amounts of Ig. Occasionally individual cells produce not one but two different classes of H chain^{39,40}; so far two types of L chain have not been found in one cell³⁹. The stable expression of two Ig classes by these immature lymphoblasts may be an artefact of culture; it may, however, reflect the multi-potentiality for C_H gene expression in virgin precursor lymphocytes.

By contrast, plasma cells express single structural genes for L and for H chains^{41,42}. A low incidence (<1 per cent) of human myeloma cases presents a double paraprotein syndrome. One case (Til) showed an IgG₂κ and an IgMκ¹⁷. These proteins were made exclusively in separate plasma cells at the time of examination¹⁷. First the κ chains of the two proteins were found to be identical¹⁷; subsequently the V regions of the γ₂ and μ chains have proved to be indistinguishable by idiotype antisera or amino-acid sequence of the first twenty-seven residues¹⁸. This fascinating finding provides good evidence for separate V and C genes but it raises more questions than it answers. To explain how one V_H gene can be expressed in separate cells in conjunction with different C_H genes, a genetic switch occurring within the clone has been suggested¹⁸. This idea is not new and can be linked with several immunological phenomena⁴³⁻⁴⁵. A phenotypic switch could also operate, implying multipotential precursor cells. A simple genotype capable of explaining the available data would result from a multiple integration step in which all C_H genes integrate with the same V gene (in *cis*)⁴⁹; this would require a copy-choice mechanism (Fig. 2). The potential of the cell at this stage would be unrestricted in respect of C gene products, class, type or allotype of Ig, but would be limited to only the small number of antibody specificities generated by combination of four different V_L sequences and two different V_H sequences. Not all of the eight possible V_L - V_H combinations would necessarily give viable molecules, and so the possible number of receptor molecules expressed at the cell surface may be even more restricted. Whatever the genetic potential of this pre-committed stem cell, there can be no selection until the phenotype is expressed; for maximum efficiency the display of receptors on the virgin precursor cell should represent all possible viable antibody molecules. A test of this proposal is afforded by the human lymphoblasts producing two H chain classes^{39,40}; there would be a high probability of the two H chains sharing the same V sequence. It remains to be seen, however, whether a switch is a rare event or a regular occurrence with the development of an antibody-forming cell clone.

In synchronized cultures of human lymphoid cells^{46,47} or mouse myeloma cells⁴⁸ the production of human IgA, IgG or IgM^{46,47} or mouse IgG_{2a}⁴⁸ has been found to be greatest

during late G1 and early S phases of the cell cycle. Ig production is essentially shut off during, and for some time before and after, mitosis. Inhibition of RNA synthesis with actinomycin D indicates that the period of Ig synthesis commencing in late G1 is dependent on the initiation of transcription of heavy and light chain genes during G1 (personal communication from D. Buell and J. L. Fahey).

Production Balance

The quantitative balance of production of L and H chains in a single cell has been discussed by several authors^{5,9,10} and I shall only briefly summarize the position. The norm is an approximate balance of chain production. This is not a rigidly maintained balance and accidental disbalance is seen relatively frequently. There does not, however, seem to be any case of disbalance with a specific function. Both extremes of disbalance, separate synthesis of either H or L chains, are found, but the latter is more common. The rate of conversion of a mouse myeloma cell line in culture from L+H production to production of only L chains has been measured as 1.1×10^{-3} /cell/generation⁵⁰. It has been pointed out that this high rate of somatic mutation may represent the additive effects of a number of less frequent events, each of which can turn off H chain synthesis independently. The screening technique⁵¹ used in this study should be useful for detecting a whole range of mutations in the Ig synthesizing machinery.

Antigenic stimulation of precursor cells results in a chain of proliferation with increasing cellular differentiation, terminating in a clone of mature plasma cells secreting a homogeneous antibody. The heterogeneity of antibody produced in the immune response to a single antigen reflects the number of clones of antibody-forming cells involved. This complexity has hampered biochemical studies of antigenic triggering. Recent studies on the selection of single antibody-forming cell clones⁵²⁻⁵⁴ should provide a more amenable system.

Monoclonal Response

Single clones have been selected by transfer of limited numbers of hapten primed spleen cells into lethally irradiated syngeneic mice. Allotype⁵³, isoelectric spectrum⁵⁴, affinity constant and hapten-binding heterogeneity⁵² have been used as phenotypic markers of single clones. A single clone of antibody-forming cells can be propagated by successive transfer of memory cells in irradiated syngeneic mice⁵⁴. By following single clones of antibody-forming cells over many generations of division it should be possible to answer many questions concerning the mutability of V genes and the stability of VC gene integration. At each transfer, proliferation of clonal cells and transformation to secreting plasma cells depend strictly on antigen. Memory cells are not short lived in the absence of antigen⁵⁴. This should make possible controlled studies on interaction between antigen and a defined precursor cell population. For this purpose, the monoclonal response can be initiated *in vitro* and studied either by culturing pieces of spleen⁵² or by transferring the cells back into irradiated hosts⁵⁴. A test of the proposed identity of receptor antibody on memory cells and secreted antibody should be possible in a monoclonal system.

Until more details are available, a hypothetical molecular mechanism for the immune response is not worth committing to print. In view of the systems available and the efforts being expended, the immune response appears to be one of the most tractable of systems for the study of differentiation mechanisms.

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Vegetation and Development of Llyn, a Welsh Mire

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An ecological survey of a newly discovered mire demonstrates the importance of historical knowledge for the formulation of management and conservation policies.

IN 1969, D. A. Goode of the Nature Conservancy discovered a mire approximately 500 m long by 250 m wide in south-west Radnorshire which had previously escaped the notice of botanists and ecologists. It lay in a hollow of soliflucted material close to the River Wye, 2 km south of Newbridge on Wye (grid reference S.O. (32) 016552). Its surface vegetation bore evident signs of lack of disturbance, being dominated by *Sphagnum* mosses with abundant lichens, and having many pine trees with tall heather beneath them which showed no sign of having been burnt in recent times.

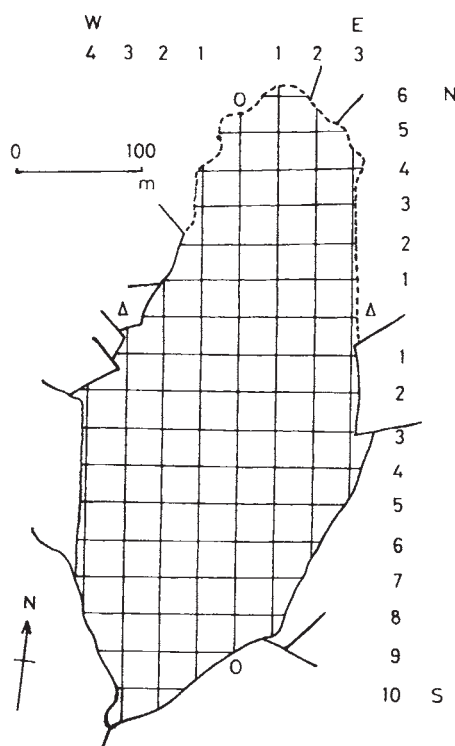


Fig. 1 Map of Llyn Mire showing the arrangement of grid lines across the bog surface.

Undisturbed bog vegetation is rare in southern Britain, and this fact, coupled with the interesting patterning and distribution of the surface vegetation on Llyn Mire, led to a detailed survey of the surface and the development of the bog. In particular it was hoped to elucidate the relationship between present day vegetation and the course of plant succession which had taken place in the basin.

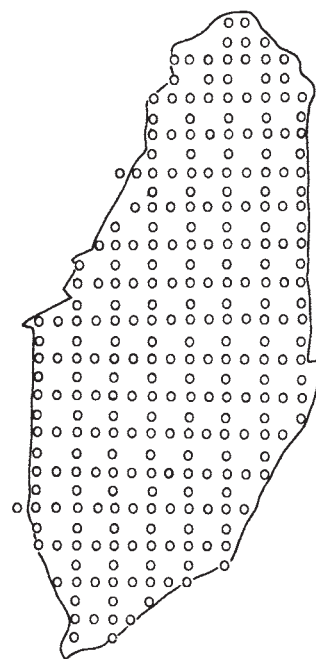


Fig. 2 Map showing the position of the 277 quadrats.

Objective description and mapping of the surface vegetation of the mire was effected by means of 0.5×0.5 m quadrats which were laid out on a grid (Fig. 1) with 30 m spacing between lines. The quadrats were placed every 15 m along these lines as indicated in Fig. 2. In all, 277 such quadrats were taken and all plant species found in each were recorded.

To map the communities, these quadrats were sorted into groups according to their floristic similarity. This involved the use of the University of London Control Data 6600 computer and the information-statistic classificatory program DIVINF of Lance and Williams¹. This program selects the species on which the quadrat population can be split to give the maximal drop in information content in the residual groups. The resulting groups can be subdivided on the

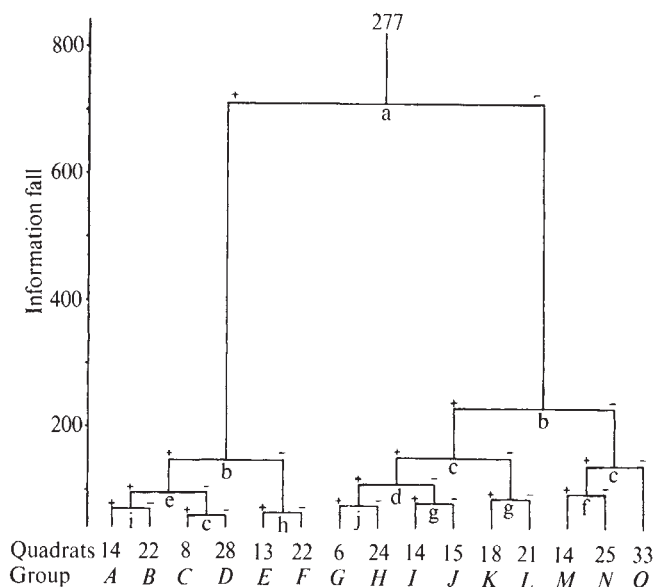


Fig. 3 Results of the analysis of quadrat data into fifteen groups. The species of plants on which the data have been split are as follows: a, *Calluna vulgaris*; b, *Molinia caerulea*; c, *Betula pubescens*; d, *Sphagnum recurvum*; e, *Pleurozium schreberi*; f, *Usnea subfloridana*; g, *Hypogymnia physodes*; h, *Pinus sylvestris*; i, *Oxycoccus palustris*; j, *Parmelia sulcata*.

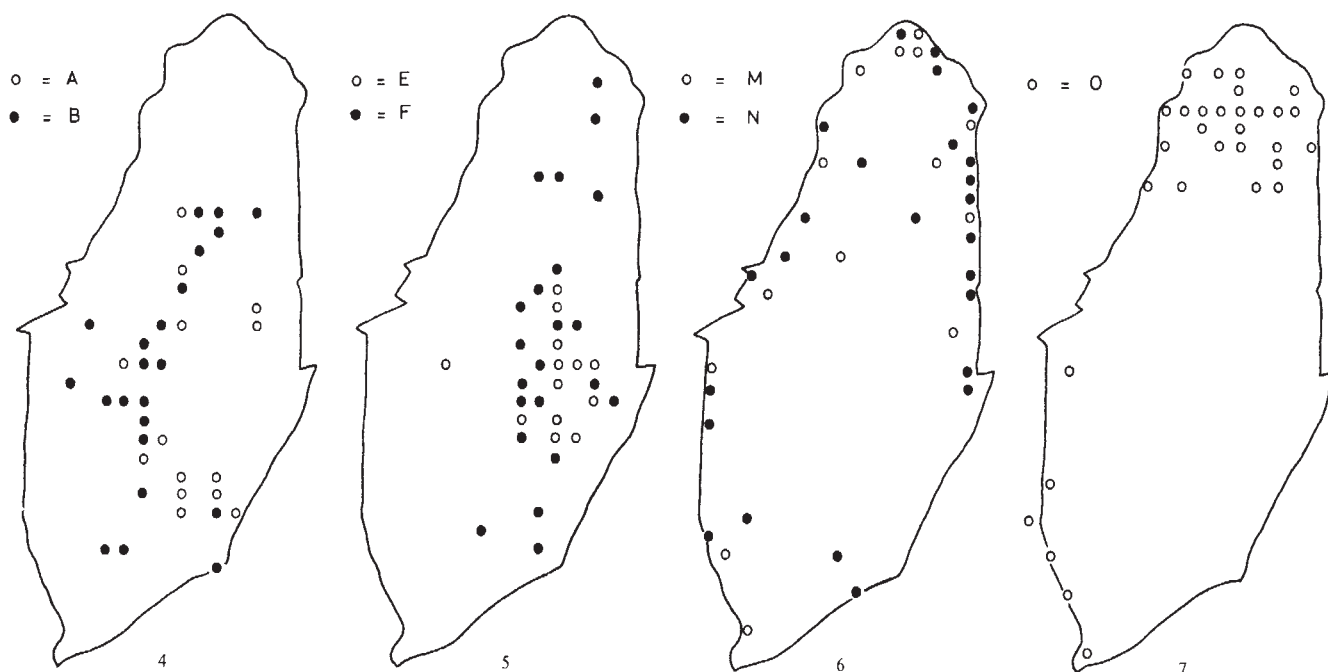
same system, providing a hierarchical breakdown of the quadrat population into a defined number of groups. Fifteen groups were obtained from this analysis (Fig. 3). Fig. 4 shows the spatial distribution of quadrats belonging to groups E and F. These show a tendency to clump in the south-eastern part of the mire. They are defined by the presence of *Calluna* and absence of *Molinia* and contain in abundance the acidophyllous species of *Sphagnum* plus *Oxycoccus* and *Erica tetralix*.

Groups A and B (Fig. 5) occupy a crescentic area surrounding E and F. They contain *Calluna*, *Molinia* and the moss *Pleurozium schreberi* and are found beneath a tall canopy of pine trees (*Pinus sylvestris*). Groups M and N have a marginal distribution (Fig. 6). They have no *Calluna* or *Molinia* but

contain *Betula pubescens*. They represent the birch carr vegetation which is particularly well developed in the northern end of the mire. Finally, group O has a distinctly northern distribution. This group is defined using negative criteria, quadrats having no *Calluna*, *Molinia* or *Betula*. The most frequent species in these quadrats is *Sphagnum recurvum*, a moss which often dominates areas which have been subjected to peat digging at some stage in their history.

This distinctive pattern of plant communities was correlated to some extent with the acidity and mineral content of surface waters. In general, samples from the group E/F region were of a lower pH and lower nutrient status than those of other areas. But a knowledge of the developmental history of the mire was an obvious prerequisite for fuller understanding of the factors underlying the vegetational pattern. The stratigraphy of the mire was therefore investigated by taking a series of peat borings, along two lines, one running north-south along grid line 0 and the other east-west along line S3. These two lines intersect at a point close to the cluster of group E/F quadrats (Fig. 4). Two profiles of the mire were constructed and are shown in Fig. 8.

These profiles show that the developmental history of the site has been complex. At the commencement of sedimentation there seem to have been three lake basins in the underlying till separated from one another by ridges; a wide, deep basin in the south-east, a smaller, deep hollow in the north and a shallower trough in the west. The succession of clays and organic silts at the base of the profiles in these basins shows the typical late-Weichselian sequence for eastern mid-Wales^{2,3}. Pollen analyses of these sediments confirm this approximate dating. Subsequently an organic detritus mud (diagonal cross-hatching) was deposited in all basins, indicating open water with an abundance of aquatic macrophytes (fruits of *Potamogeton* spp. are particularly abundant). Invasion of reed-swamp and fen vegetation followed, completely obliterating open water in the northern and western basins, where the hydrosere continued, resulting in swampy woodland. Development in the south-east basin, however, followed a rather different pattern. Here the invasion of reedswamp from the north and west was incomplete and was followed by reflooding of much of the swamp and even some of the carr woodland. This rise in the water level in the south-east may well have been a direct result of the silting of the northern basin. Present



Figs. 4-7 Distribution of selected quadrat groupings on the surface of the mire.

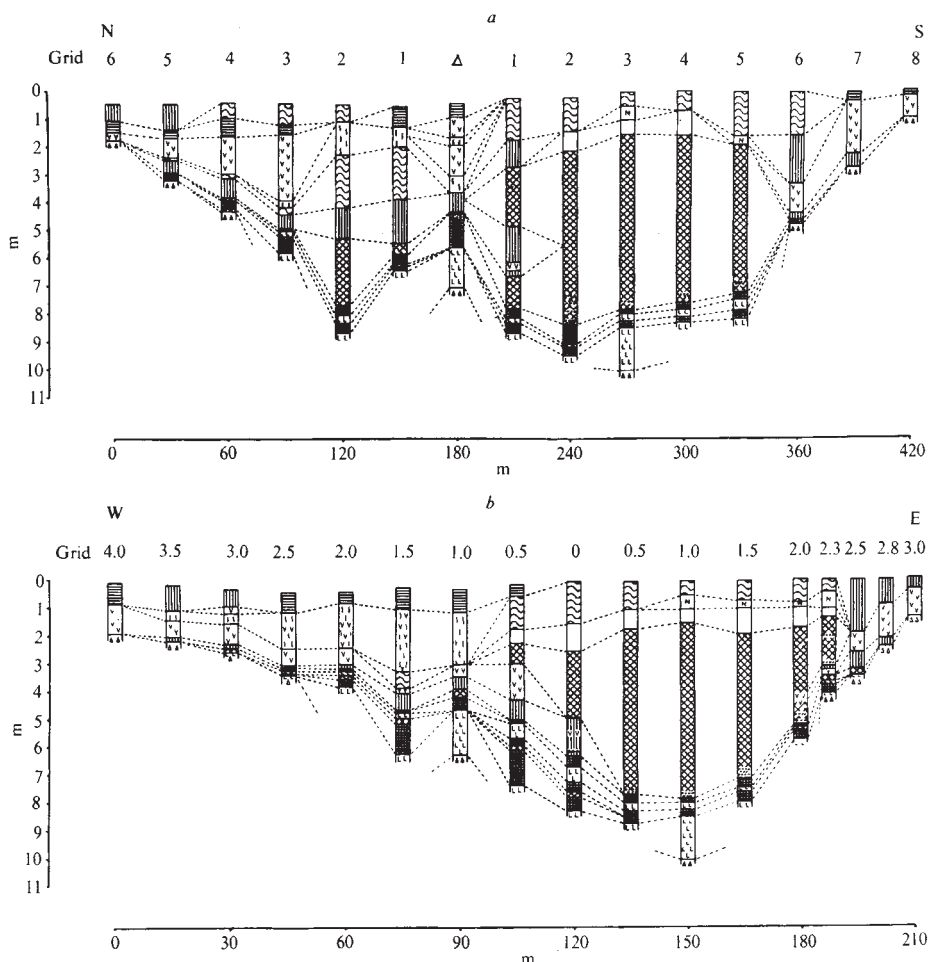
drainage of the mire is to the north and it is likely that this was so throughout its development. If this were the case, the infilling of the northern basin could have restricted the drainage of the lake in the south-east and caused the rise in water level.

Peat stratigraphy in the north and west above this point shows signs of disturbance, almost certainly due to peat cutting. There is some surface evidence of this, particularly in the north where the top layers of peat seem to have been stripped off uniformly, the regenerating vegetation being of group O type (Fig. 7). There is also local historical confirmation of such digging.

as that at Llyn. In the eastern United States there are many examples⁷.

The peripheral birch carr (groups M and N, Fig. 6) seems to have existed at the site since an early stage in mire development. It is perhaps its age and historical continuity which account for the rich epiphytic lichen flora of the carr, some species, for example *Cetraria sepincola*, being scarce and of disjunct distribution. The pine woodland, however, seems to be a recent introduction. Pine pollen is abundant in the floating bog vegetation but is very scarce in the upper lake sediments. Perhaps it spread during the period of peat cutting.

Fig. 8 The stratigraphy of Llyn Mire. *a*, Grid line 0; *b*, grid line S3. Triangles, till; vertical cross-hatching, silty mud; diagonal cross-hatching, organic lake mud; L, clay; vertical lines, fen peat; horizontal lines, *Molinia* peat; V, wood peat; wavy lines, *Sphagnum* peat; N, rhizomatous peat; broken vertical lines, *Eriophorum vaginatum* peat.



Development in the south-east was quite different. Here the lake continued to exist until it was eventually enveloped by a floating mat of aquatic vegetation to produce the quaking bog which exists there now (quadrat groups E and F, Fig. 4). One metre below the present bog surface there is still a metre of water before the gelatinous lake detritus is reached. Pollen analysis of the surface mat and of the detritus has helped to date the final invasion of this lake by floating bog. The lake sediments contain many pollen indicators of cultivation, especially *Cannabis sativa*, which is known to have been grown in the Cheshire area in medieval times⁴. Lake invasion, therefore, is likely to have occurred during historic times (the name "Llyn", Welsh for lake, also suggests this) and probably in the post-medieval period.

This type of bog development (termed *schwingmoor* by the Germans) is unusual in Britain. Chartley Moss, Staffordshire, Clarepool Moss, Cheshire⁵, and Wybunbury Moss, Cheshire⁶, show rather similar developments over kettle-hole lakes, but are probably not such good examples of the hydrosere sequence

as that at Llyn. In the eastern United States there are many examples⁷. It is evident from this study of Llyn Mire that the vegetation of such wetland ecosystems can only be understood by reference to their developmental histories. Such an understanding is essential for their management and conservation.

This work was carried out at the instigation of the Nature Conservancy, which financed the field work. Much of the work in the field was performed by H. Ireland, P. Gregory, R. A. Armstrong and B. Rayner. The program DIVINF was supplied by Drs W. T. Williams and G. N. Lance and was modified by Dr R. S. Clymo.

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Plasma Testosterone, Dominance Rank and Aggressive Behaviour in Male Rhesus Monkeys

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An animal's plasma testosterone is related to its dominance rank and the frequency of aggressive behaviour exhibited in a social group.

CONSIDERABLE interest has developed in the relationship of testosterone to aggressive behaviour. This hormone must be present during crucial periods of brain development for the appearance in the adult of male sexual and aggressive behaviour¹⁻⁵, but nothing is known of the relationship between normal aggressive behaviour associated with living in social groups and the level of endogenously secreted testosterone. This relationship is of interest in two ways. First, testosterone secretion is susceptible to environmental influences by means of the hypothalamic-pituitary-gonadal system⁶⁻⁷. Second, aggressive behaviour may be effected by changes in brain concentration of testosterone, secondary to increased or decreased secretion⁸⁻¹¹.

Conditions of Captivity and Experiment

Thirty-four male adult rhesus monkeys were placed in a large outdoor compound measuring 125' x 125', with access to an enclosed, temperature-regulated building for shelter; food and water were freely provided. These conditions permitted careful observation and recording of all interactions between animals, as well as providing more than one-third of an acre to allow animals to keep separate. Females were excluded so that the possible effect of differential sexual activity would not confuse any relationship observed between testosterone and aggressive behaviour.

Behavioural data were collected in formal sessions consisting of 1,000 s per animal repeated ten times during 3 months. During these sessions, behaviour was recorded using a standard inventory describing seventy-three different activities, including all social interaction as well as individual (self-directed) activities. Data on nearly 8,000 responses were transferred

to cards and computer analysis was performed to list the instigator and recipient of all dyadic interactions, as well as total frequencies of every response for every animal. The status hierarchy in the group was also analysed, based on the classical "peck order" description of dominance¹²⁻¹³. An essentially linear hierarchy was produced.

The experiment began in September 1969 and lasted for 9 months. During the first month the dominance hierarchy was established and allowed to stabilize. Behavioural data were collected for the next 3 months, that is, the second to fourth. During the fifth and sixth months, animals were repeatedly caught and released immediately in an attempt to adapt them to the procedure for collection of plasma samples. It was possible to capture and restrain every animal within 10 min. In the seventh month, animals were caught, restrained in a squeeze cage for venipuncture of the saphenous vein and 10 ml. of blood collected. The dominance rank order was again determined and found to be stable during this period, seventh month against eighth, $\rho=0.91$, eighth against ninth, $\rho=0.98$.

Blood was drawn in a 1.5 h period from 0900 h to 1030 h. The testosterone was analysed in 1.0 ml. of plasma, using a slight modification of the competitive protein-binding technique described by Mayes and Nugent¹⁴. Plasma cortisol was also analysed in each sample by the method of Murphy¹⁵ to provide a rough estimate of the degree of arousal or stress experienced by the animals during capture and venipuncture.

Aggressive behaviour comprised only 1.85% of the total behaviour observed. Of all aggressive behaviour, 80% was non-contact, which consisted primarily of threats and chase. Threats to other animals were the most frequent (56% of the total aggressive inventory): contact aggression was very infrequent (only 0.37% of total behaviour). Out of a total of approximately 8,000 behaviour observations made during the 3 months, there were only seventeen cases of slapping, six of unilateral attack, consisting of a combination of pulling and biting, three of mutual fighting, two of discrete biting and one of pulling. This is consistent with other reports that dominance rank in well established groups is maintained primarily by threat gestures and submissive responses, although physical fighting is rare¹⁶⁻¹⁷.

Testosterone Concentrations

The mean plasma testosterone concentration for the thirty-four animals was 669 ng/100 ml. of plasma, $\sigma=303$ ng%, ranging from 200 to 1,560 ng%. This is higher than reported by Resko¹⁸, but the adult males which he studied were housed indoors in individual cages.

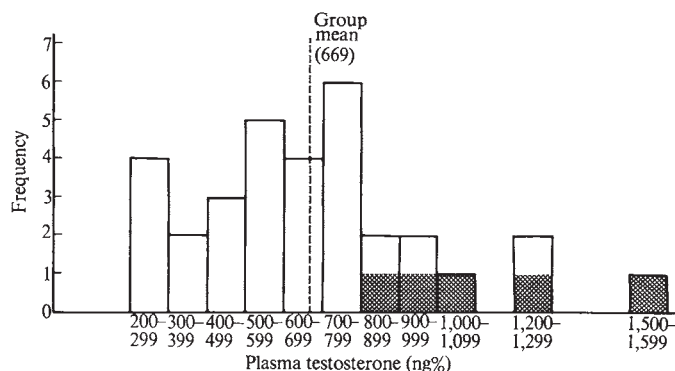


Fig. 1 Histogram of the plasma testosterone of thirty-four animals. The five animals shown as shaded squares have the highest frequency of aggressive behaviour, defined as those which exceeded the mean value by more than 1 s.d.

A histogram of the distribution of testosterone concentrations is shown in Fig. 1. The animal with the highest value of 1,560 ng% was the β male (second in dominance rank) in the group. In the first few minutes after animals were released into the compound, he formed an alliance with the animal which became the α (most dominant) male. He was clearly the more aggressive of the pair, frequently attacking other animals, but the α male showed much less frequent contact aggression. The β male remained one of the most aggressive animals during the subsequent months. The five animals shown as shaded squares were the most aggressive in the group, all exceeding by 1 s.d. the mean frequency of aggressive behaviour.

Aggression Correlation

Correlations between plasma testosterone and various agonistic categories are listed in Table 1. Aggressive behaviour, mostly non-contact in the form of threat and chase, correlated positively and significantly with testosterone concentration. Being submitted to also correlated significantly with plasma testosterone. Aggression and being submitted to were related ($r=0.543$), but do not measure the same thing, because the inverse relationship of high submissiveness and low testosterone does not seem to be very strong. Animals which showed frequent submissive responses did not have significantly lower testosterone concentrations. These relationships suggest that any animal below the α male with a high frequency of aggressive behaviour to his subordinates will tend to have higher testosterone concentrations regardless of how frequently he is submissive to the animals above him in the dominance hierarchy. Testosterone therefore seems to be more related to the frequency of aggressive behaviour than to the opposite and reciprocal behaviour of submissive responses.

Behaviour interpreted as indicative of general tension was also significantly correlated with testosterone, $r=0.534$. Responses in this category included yawning, teeth grinding, demonstrating (shaking or banging of objects) and involvement as third party in agonistic episodes. Animals with inhibited aggressive behaviour in the presence of more dominant animals may exhibit tension responses.

Dominance Correlation

Dominance rank was positively correlated with testosterone concentration. As shown in Fig. 2, the animals in the highest

quartile (rank order one to eight) had significantly higher testosterone ($P<0.05$) than animals lower in dominance. There were no significant differences observed between animals in the second, third or fourth quartiles.

Table 1 Testosterone and Behaviour

A Testosterone and behavioural correlations	
Total aggression	0.469
Non-contact aggression	0.515
Receives submission	0.516
Tension	0.534
Dominance rank	0.350 (rho)
Submission	-0.320 NS
B Behavioural intercorrelations	
Aggression and receives submission	0.543
Aggression and dominance rank	0.710 (rho)
Submission and dominance rank	-0.650 (rho)
Aggression and tension	0.334 NS
Tension and dominance rank	0.490 (rho)

All correlations listed are Pearson's r except those shown as ρ , which are Spearman's rank order correlations. All are significant to at least $P<0.05$, except those followed by NS. For all correlations, $n=34$.

Animals either higher in dominance rank or showing more frequent aggressive behaviour tend to have higher plasma testosterone concentrations. Although related, however, total aggressive and submissive responses are clearly not merely a reflexion of dominance status. The most aggressive animals in the group are not always the most dominant, nor are the least aggressive necessarily lowest in dominance. For example, the α male was twelfth in the rank order of frequency of aggressive behaviour and the animal showing the most frequent aggressive behaviour was tenth in the dominance rank. Furthermore, the α male had a testosterone concentration of 980 ng%, although the most aggressive animal, tenth in dominance, had a value of 1,290 ng%.

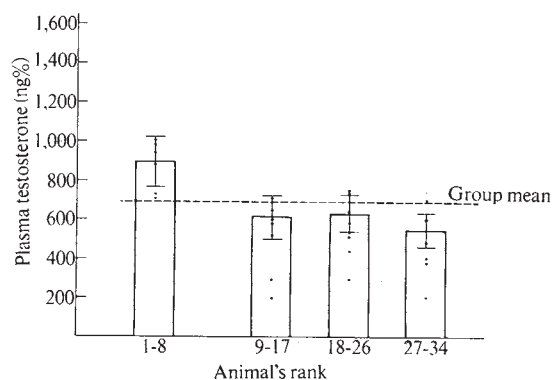


Fig. 2 Mean $\pm$ s.e. for each quartile of the dominance rank order. The most dominant animals, rank order 1-8, had significantly higher testosterone concentrations than those in the lower quartiles.

The mean plasma cortisol was 18.5 μ g%, $\sigma=6.9\%$. It is very difficult to assess accurately adrenal cortical activity from a single plasma value because of diurnal variation and episodic secretion of cortisol¹⁹. The values which we found were slightly higher than those observed in quiescent animals; however, they were not representative of the responses seen during acute stress (in excess of 40 μ g%). Moreover, animals with lower levels of

testosterone did not have higher cortisol values ($r=0.129$, NS). Thus, we are not simply observing an inhibition of testosterone in those animals more stressed by capture and venipuncture procedures. Size also does not account for differences in plasma testosterone. All animals except one were judged fully adult by dental standards and, although body weight ranged from 15 to 28 lb, there was no correlation with plasma testosterone ($r=0.186$).

A consistent relationship seems to emerge between testosterone and aggression, as measured by various specific behaviours, as well as dominance status. The correlations are significant, but only account for approximately 20–25% of the total variance. Plasma testosterone does exhibit some diurnal variation, although considerably less than cortisol²⁰. Plasma testosterone accurately reflects differences in the amount of testosterone produced daily only assuming constancy of the metabolic clearance rate among animals^{21,22}. This must be determined by direct measurement. Further studies of the stability of plasma testosterone, together with measurement of rate of production of testosterone, would clarify these issues. An important question raised by these data is whether the higher plasma testosterone concentration that is frequently seen in more aggressive animals precedes, or is the result of, their dominant and aggressive status. Anecdotal information suggests that in this group, plasma testosterone concentrations are a function of dominance and aggressive behaviour, and dominance changes alter testosterone concentrations. Studies are in progress to clarify this issue.

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Pressure Reversal of Anaesthesia

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The application of high hydrostatic pressure will remove, at least partially, the effects of general anaesthetics in both newts and mice. This feature seems to be common to all general anaesthetics and a simple model could explain this antagonism.

THE first observation of the effects of hydrostatic pressure in modifying the response of organisms to drugs is due to Johnson and Flagler¹. Having observed that the application of pressure could restore the luminosity of luminous bacteria that had been exposed to an anaesthetic agent, they tried a similar experiment on tadpoles narcotized with ethyl alcohol. The effect of 2–5% alcohol is to narcotize the animals so that they cannot swim and fall to the bottom of the vessel. In the absence of the

alcohol the tadpoles responded to pressure by increased activity at 130 atmospheres and exhibited paralysis at about 300 atmospheres. If a pressure of 200–300 atmospheres is applied to the anaesthetized tadpoles they resume swimming in an apparently normal manner. Similar results are reported here for newts and mice using the narcotic or anaesthetic gases N₂ and SF₆, a barbiturate anaesthetic and two common clinical anaesthetics, ether and halothane.

The effects of high hydrostatic pressures alone on living organisms have been under active investigation for almost a century². The classic work of Regnard³ and subsequently Ebbecke, Cattell and others showed that the first effect of pressure on aquatic animals is to stimulate the central nervous system; this happens above 50 atmospheres⁴. At higher pressures (200–300 atmospheres) spontaneous muscle contraction occurs and the animals become paralysed. Still higher pressures (about 400 atmospheres) are lethal. In experiments with mammals, it is not always easy to distinguish between the effects of pressure as such and the narcotic effects of the gases breathed. Thus Italian newts lose their ability to right themselves at pressures between 165 and 245 atmospheres

whether the pressure is applied with helium or neon, or even hydrostatically⁵. Newts and mice have been shown to be similarly susceptible to anaesthesia by nitrogen, but mice exposed to high pressures of helium and neon are not anaesthetized even though both gases proved lethal at 135–145 atmospheres. This is the origin of the view that helium (and perhaps neon) have anaesthetic pressures for mice and newts greater than the tolerable mechanical pressures, and that these gases can be used to study the effects of pressure as such on mammals.

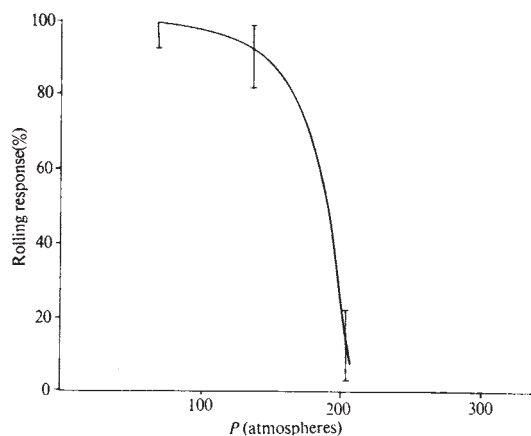


Fig. 1 Rolling response of newts as a function of hydrostatic pressure (in water). Error bars indicate the 95% confidence limits. Ten animals were used in the experiments. The temperature was 20° C, and the rotation speed was 4 r.p.m.

The results of experiments so far indicate that there are four principal effects of hydrostatic pressure on mice^{6–8}. (i) Uncoordinated tremors (onset 70 ± 10 atmospheres) which may depend on the rate of compression; (ii) convulsions—which have been observed at somewhat higher pressure by most but not all investigators; (iii) respiratory distress at pressure above 90 atmospheres, and (iv) paralysis.

Experiments with Newts

To investigate the effects of pressure and anaesthetics we have carried out further studies on the Italian crested newt (*Triturus cristatus carnifex*), which can be exposed to hydrostatic pressure both directly (in water) and using a gas. It resembles the mouse in having a rapid righting reflex and it shows a similar sensitivity to anaesthesia in the presence of simple gases. The experiments were carried out in a high pressure cylindrical chamber of 0.3 l. volume fitted with a window at one end. The chamber could be rotated at four revolutions per minute and the ability of the animals to follow the revolutions (rolling response) observed. The animals which rolled over completely during any one revolution were ascribed a zero score; all others scored one. Sets of five revolutions were observed and a final performance recorded as a percentage score. Failure to respond could arise either from the effects of narcosis or from the impairment of movement produced by very high pressures above 140 atm. The experiments were carried out at 20° C and the partial pressure of oxygen was initially 1 atmosphere. This provided sufficient oxygen for mice to survive for 3 h. Newts proved considerably less sensitive to anoxia than mice; nevertheless observations were restricted to the first 90 min. A soda-lime canister which could be moved up and down the chamber was used to keep the partial pressure of CO₂ below 1.5 mm Hg.

The first series of experiments were carried out using hydrostatic pressure alone. The pressure vessel was filled with

water and no free gases were present. As the pressure is raised occasional failure to follow the revolutions of the chamber is observed at 100 atmospheres and the failure is almost total at 200 atmospheres. Exposure to high pressures of helium and neon gave rise to similar responses although there is evidence that the onset of the adverse effects occurs at somewhat higher pressures than with hydrostatic pressure alone (Figs. 2 and 3).

To investigate the antagonism between pressure and anaesthetic agents a further series of experiments were carried out with newts that had been anaesthetized with 34 atmospheres of nitrogen. In this condition they were unable to respond to the rotation of the chamber. But when they were subjected to higher pressures by the addition of helium, this ability was almost completely restored at 140 atmospheres. Further increase in the pressure led to a subsequent decline in the rolling response, but even at almost 300 atmospheres the response was at the 50% level (Fig. 4).

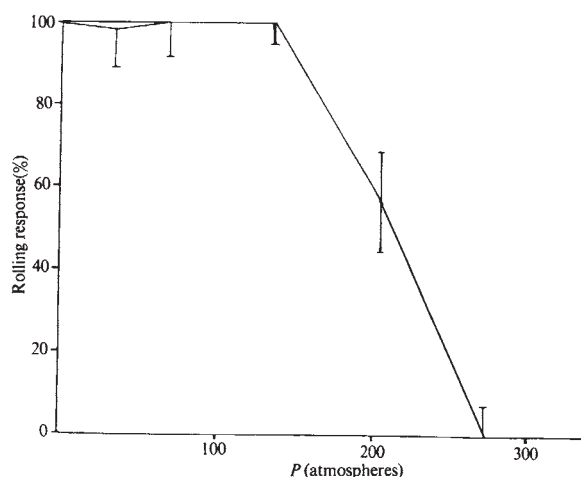


Fig. 2 Rolling response of newts as a function of helium pressure. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

To demonstrate that the narcosis is antagonized by pressure *per se* and not by some interaction specific to helium, experiments were performed in which the pressure was raised mechanically (no gas phase being present). Newts were totally immersed in sodium pentobarbitone solution (0.4 mg/ml.) in the pressure chamber. When the hydrostatic pressure was raised to 140 atmospheres the rolling response increased from 4% to 56%. Similar antagonism between anaesthesia and hydrostatic pressure has also been demonstrated in preliminary experiments on ether (32 mM), halothane (1.15 mM) and butanol (28 mM) in aqueous solution.

Experiments with Mice

The experiments were carried out in a 1.5 l. chamber capable of working to pressures of 300 atmospheres. The internal dimensions of the chamber which was closed with a Graylock seal were 20 cm by 10 cm. The interior could be observed through two 1 inch diameter toughened glass windows. Gas at pressures greater than those in the supply cylinders was obtained from a compressed air driven pressure intensifier. The mice were exposed in pairs in large mesh wire cages. A powerful fan driven by an induction motor ensures mixing of the gases (a serious problem at very high pressures) and CO₂ removal at the scrubbers. The initial partial pressure of oxygen was adjusted to 1 atmosphere and was not allowed to fall to less than 0.5 atmospheres during the experiments. The chamber was maintained at a temperature of $30^\circ \pm 3^\circ$ C. In the case of mice the effects of high pressure are to some extent

dependent on the rate of compression. The pressures at which tremors and convulsions are first observed at compression rates varying by a factor of twenty are given in Table 1. Approximately half the deaths reported in Table 1 were associated with convulsions; the remainder either occurred suddenly or, especially at the higher pressures, after a moribund period. The cause of death when not associated with convulsions was not obvious. To investigate whether respiratory distress was a contributing factor a series of comparative tests with neon was carried out. The molecular weight, and thus the density at any given pressure, of neon is five times that of helium. Mouth breathing was observed above 95 atmospheres, but although respiratory distress was more marked than with helium the lethal threshold was not significantly different (Table 2). Furthermore, mice exposed to high pressures (20 atmospheres) of CF₄ (ref. 10) have survived in a gas density nearly three times that at which death occurs with helium. Even under slow compression, the pressure which proves lethal for mice produces only a 10–15% diminution in the ability of newts to follow the revolutions of the chamber (Table 3). The greater sensitivity of mice to high pressure could be due to their absolute dependence for life on rhythmic cardiac and respiratory muscular activity.

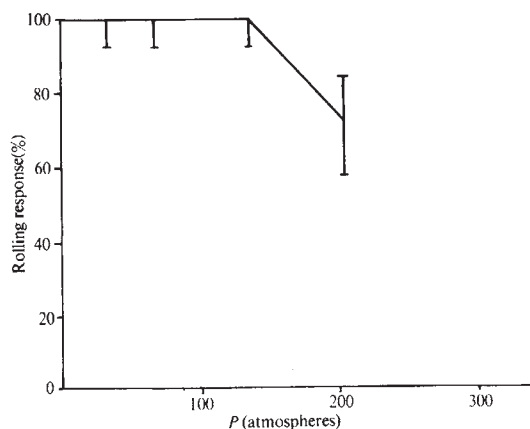


Fig. 3 Rolling response of newts as a function of neon pressure. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

In spite of these effects of pressure the reversal of anaesthesia was observed in mice. Thus when mice anaesthetized with 45 atmospheres of nitrogen were subjected to further compression with helium the anaesthesia was reversed and the animals exhibited spontaneous activity again just as in the case of newts. Similar success was obtained with mice anaesthetized with sodium pentobarbitone (0.1 mg/g subcutaneously). Furthermore, in these conditions tremors and convulsions were less distinct and both agents produced a significant increase in the lethal pressure (Table 2).

Site of Anaesthetic Action

Recent studies^{9–11} have tended to point to hydrophobic regions within the body as the site of action of anaesthetics and have lent little support to the "hydrate" theories of Pauling¹² and Miller¹³. The results are consistent with the lipid solubility model which supposes that anaesthesia occurs when a chemically indifferent substance attains a critical concentration in the cellular lipids¹⁴. This concept may be extended to account for the effects of pressure and temperature. It is proposed, following many earlier workers¹⁵, that the important action of anaesthetic molecules is to modify the dimensions of lipid regions, possibly those in cellular mem-

Table 1 Effect of Compression Rate

Compression rate (atm/min)	No. of mice	Threshold pressure (atmospheres)		
		Tremor	Convulsion	Death
10	3	35–50	70–80	136 ± 6
1.25	9	60–100	95–120	135 ± 3
0.5	3	75–109	105–120	159 ± 4

Inert gas: helium. Po₂: 0.5–1.0 atmospheres. Temperature: 30° ± 3° C.

Table 2 Experiments with Mice at Very High Pressures

Inert gas	No. of mice	Threshold pressure (atmospheres) ± s.d.		
		Tremor	Convulsion	Death
He	9	74 ± 8	108 ± 4	135 ± 3
Ne	6	88 ± 3	130 ± 7	144 ± 11
With anaesthetic				
He + 45 atm N ₂	4	—	—	166 ± 3
He + barbiturate*	4	—	—	200 ± 6

Po₂: 0.5–1.0 atmospheres. Temperature: 30° ± 3° C. Average compression rate: 1.25 atmospheres/min.

* 0.1 mg/g Na pentobarbitone.

branes. Anaesthetic potency would then be proportional to the product of the solubility of the agent in lipids and its partial molar volume. (It has not proved possible to distinguish this model from one in which potency is simply proportional to fat solubility using available experimental data since molar volumes vary over too narrow a range compared with the variation of solubility.) The site of action of anaesthetics corresponds to a region of solubility parameter $\delta = 9 \pm 1$ (calories cm⁻³)[†] where

$$\delta = \left(\frac{-E^{\text{vap}}}{V} \right)^{\frac{1}{2}}$$

and E^{vap} is the energy of vaporization and V the molar volume of the solvent region^{9,10}. This value of the solvent power can be used to estimate other physical properties of the region. Thus for a van der Waals fluid

$$\delta^2 = \left(\frac{\partial E}{\partial V} \right)_T = T \left(\frac{\partial P}{\partial T} \right)_V = T \frac{\alpha}{\beta}$$

where α is the coefficient of thermal expansion and β the coefficient of isothermal compressibility. For a solvent for which $\delta = 9$ (calories cm⁻³)[†], changing units gives $\delta^2 = 3,320$ atmospheres; then

$$\left(\frac{\partial P}{\partial T} \right)_V = \alpha/\beta = 11 \text{ atmospheres deg}^{-1}$$

that is, an 11 atmosphere rise in pressure at the temperature concerned, would be required to nullify the expansion caused by a 1° C temperature rise. Assuming a reasonable value for α of, say, $\sim 0.5 \times 10^{-3} \text{ deg}^{-1}$ would lead to an estimate for β of $\sim 5 \times 10^{-5} \text{ atmosphere}^{-1}$. (For benzene at 25° $\alpha = 1.2 \times 10^{-3} \text{ deg}^{-1}$ and $\beta = 9 \times 10^{-5} \text{ atmosphere}^{-1}$; for olive oil at 15° $\alpha = 0.7 \times 10^{-3} \text{ deg}^{-1}$ and $\beta = 6 \times 10^{-5} \text{ atmosphere}^{-1}$ (refs. 16, 17).) The critical anaesthetic concentration in the lipids can be estimated to be $\sim 0.05 \text{ M}^{18}$, and because the partial molar volumes²⁰

of anaesthetics are in the range 50–100 cm³ an anaesthetic dose would produce an expansion of lipids of the order of 0.4%. Using the estimated value of β the pressure increase required to nullify this expansion can now be calculated to be of the order of 100 atmospheres. This is consistent with the pressures experimentally required to remove the effects of a normal anaesthetic dose. It follows from the model that the pressure required should be directly proportional to the partial molar volume of the anaesthetic agent and the dose used. The results of preliminary experiments suggest that these consequences of the model can be seen. Thus if newts are anaesthetized with 68 atmospheres of nitrogen (twice the anaesthetic dose used in the experiment described earlier) the recovery of the rolling response at 140 atmospheres total pressure (N₂ + He) is only about 50%. Similarly, preliminary experiments show that 140 atmospheres pressure only produces a 50% recovery in newts exposed to a normal anaesthetic dose of SF₆ (ref. 19) (estimated molar volume 76 ml. whereas that of nitrogen is 35 ml. (ref. 15); the partial molar volumes in benzene ($\delta=9.2$) are 97 ml. and 53 ml. respectively²⁰). An interesting prediction can be made that hydrogen would be the most successful gas to use at high pressures, the expansion due to its solution being almost exactly balanced by the compression due to pressure.

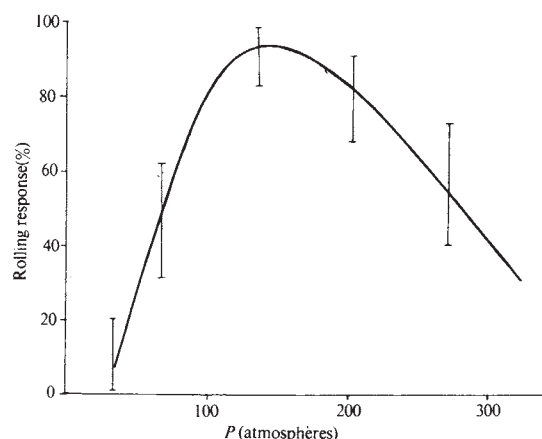


Fig. 4 Rolling response of newts as a function of helium pressure in the presence of 34 atmospheres nitrogen. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

It is a further consequence of the model that cooling by $\sim 10^\circ\text{C}$ should antagonize the effects of normal doses of anaesthetics. With whole animals the predominant effect of lowering the ambient temperature is hypothermia (which results in loss of activity in goldfish at 2°C) (ref. 21). Where higher doses of anaesthetics are required at low temperatures the explanation most readily given is in terms of changing solubility relations²². But Spyropoulos²³ showed that the reduction in the action potential in a toad single nerve fibre induced by application of a 3% ethanol solution could be removed by cooling by 15°C or by applying 500 atmospheres

pressure. The reversal of anaesthesia by pressure in luminous bacteria has already been noted. A further feature of the bacterial system which is in keeping with the simple model we propose is that if the bacteria are above their optimum temperature for luminescence the application of hydrostatic pressure will increase the level of luminescence²⁴.

It is not possible to define precisely where the lipid region involved in anaesthesia is located but two areas could be important. First, hydrophobic areas within certain specific enzymes have been proposed as the site of action of anaesthetics, for example such an area has been invoked to explain the action of competitive inhibitors on α -chymotrypsin²⁵. Furthermore, the response of luminous bacteria to anaesthetics and the antagonism of this response by high pressures has been interpreted in terms of the effects of these agents on the enzyme responsible for the luminescence, luciferase. No enzyme sufficiently sensitive to anaesthetics has yet been identified in the central nervous system however. Second, there are the lipids of the cell membrane where various actions could take place. Distortion or disordering induced by the anaesthetic could reduce control of or alter permeability; some workers have suggested that anaesthesia results from increased permeability^{26,27}, and others that it results from decreased membrane permeability²⁸. It is possible that the disturbance of the lipid part of the membrane is transmitted to some functionally vital protein in such a way as to render it inoperative.

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Table 3 Comparison of Mice and Newts

	Lethal limit for mice (atm)	% RR of newt at this pressure
He	159	85
N ₂	(159)	90
He-N ₂	166	92

LETTERS TO NATURE

PHYSICAL SCIENCES

Two New Point Sources of High Energy Cosmic Gamma Rays

MORRISON¹ was the first to suggest that certain astronomical objects might emit a measurable flux of γ -rays. By the middle of the last decade much theoretical work had been done on the flux to be expected from neutral pion decay, inverse Compton collisions and bremsstrahlung²⁻⁶. Evidence for the detection of such a point source of cosmic γ -rays above 50 MeV, Sgr γ -1, was reported by the CWRU-Melbourne collaboration⁷ and Fazio⁸ reviewed high energy γ -ray astronomy in early 1970, but as far as we know, no other observation of this source has been made at γ -ray, X-ray or longer wavelengths. The identification of Sgr γ -1 was based on preliminary analysis of spark chamber data from two high altitude flights in Australia and a third flight has confirmed this source. The combined data from the three flights make possible the identification of two other point sources of high energy γ -rays which agree in position with known hard X-ray sources. We find no evidence on any flight for a diffuse line source along the galactic plane.

The operational parameters for the three balloon flights are listed in Table 1. Flight III was made at a higher geomagnetic cutoff, which resulted in a reduction in the intensity of the atmospheric background γ -rays to 0.69 that of the first two flights. The data from the three flights were combined and analysed as described previously^{9,10} by two equal area projection methods which gave good agreement. The one discussed here plotted density against right ascension and sine declination with a basic bin size of $1^\circ \times 0.02$. Both resolved pairs and non-scattering single tracks, that is R (rectilinear) tracks, were used¹⁰. To search for point sources above the atmospheric background a computer program was written which provided a contour output by summing over a 4×4 bin the centre of which was shifted in 1° and 0.02 steps. In addition to Sgr γ -1 two directions were found where the number of γ -rays exceeded the atmospheric background by at least four standard deviations. Moreover, the two directions agree with the location of the two hardest X-ray sources seen by Lewin *et al.*¹¹ in a survey of this region. Both of these sources lie near the galactic plane, so we will follow the convention established for the galactic X-ray sources and designate them as G γ 2+3 and G γ 341+1.

There are three principal pieces of evidence for a source of cosmic γ -rays (G γ 2+3) near the galactic centre. (1) The

excess of events for the three flights combined is 4.4σ above the atmospheric background, which was obtained as the average over the $\Delta\alpha=28^\circ$, $\Delta \sin \delta=0.56$ rectangle centred at the source position (Table 2). In the region $220^\circ < \alpha < 310^\circ$, $-59^\circ < \delta < -6^\circ$, the probability of finding one $4^\circ \times 0.08$ bin with this excess is $\approx 10^{-3}$. (2) A signal of at least 1σ was seen on each of the three flights at a position whose α and δ differed by at most 1.2° from the mean position. This excess of events on each flight plus the fact that two different gondolas were used provide some assurance against systematic errors. (3) Perhaps the most conclusive evidence is that the mean position $l=2.0 \pm 1^\circ$, $b=+3.4 \pm 1^\circ$ agrees well with that of the hard X-ray source found by Lewin *et al.*¹² at $l=1.4 \pm 0.5^\circ$, $b=+4.0 \pm 0.5^\circ$. We cannot exclude the X-ray source GX 3+1 whose position has been reported as $l=2.29 \pm 0.03^\circ$, $b=+0.79 \pm 0.03^\circ$ (ref. 13), and $l=2.17 \pm 0.15^\circ$, $b=+1.95 \pm 0.15^\circ$ (ref. 14), but the positional agreement with GX 1+4 is better and it has a harder spectrum than GX 3+1 (ref. 12).

Our positional accuracy is sufficient to exclude the galactic centre itself, which is a strong radio and infrared source but has not been observed to emit X-rays.

Buselli *et al.*¹⁵ have fitted their observation of the X-rays above 20 keV from this direction with the power law $N(E)=3.4 E^{-2.0 \pm 0.2}$ photons $\text{cm}^{-2} \text{s}^{-1} \text{keV}^{-1}$ in agreement with Haymes *et al.*¹⁶ who report $N(E)=2.8 E^{-2.20 \pm 0.35}$. Our integral flux of $(1.5 \pm 0.5) \times 10^{-5} \text{ } \gamma\text{'s cm}^{-2} \text{s}^{-1}$ for $E_\gamma > 100 \text{ MeV}$ can be fitted to the same power law if the exponent is taken as -2.05 . It is remarkable that the same exponent found in the X-ray region should fit so well when extrapolated three decades in energy. Of course there could be a steepening of the spectrum above 100 keV, and the flux found here could be due to a separate broad peak from neutral pion decay. Spectral measurements in the region below 100 MeV are needed to see if a neutral pion bump exists and thus to identify the γ -ray production mechanism.

A statistically significant number of events is found above 500 MeV yielding a flux of $(4 \pm 2) \times 10^{-6} \text{ } \gamma\text{'s cm}^{-2} \text{s}^{-1}$ which is also consistent with the same power law extrapolation.

A source of somewhat similar characteristics has been found at the position $l=340.9 \pm 1^\circ$, $b=+0.8 \pm 1^\circ$ (G γ 341+1). It is at least 2σ above atmospheric background on each flight. The location is in agreement with that of the second hardest X-ray source at $l=340 \pm 3^\circ$, $b=-2 \pm 3^\circ$ found by Lewin *et al.*¹¹ in the portion of their survey area which overlapped ours ($220^\circ < \alpha < 280^\circ$). G γ 341+1 also agrees in position with the lower energy X-ray source GX 340+0 reported at $l=340.0 \pm$

Table 1 Operational Parameters of the Balloon Flights

Flight	Launch site	Geomagnetic cutoff	Flight duration at altitude	Average altitude ($\pm \sigma$ mbar)	Max. alt.-min. alt. (mbar)
I	Parkes, NSW, Australia. Lat. $\approx 33^\circ$ S	4.5 GV	Feb. 5-6, 1969. 2136-0207 UT	2.86 ± 0.13	2.67-3.05
II	"	4.5 GV	Feb. 26-27, 1969. 1815-0205 UT	2.98 ± 0.17	2.84-3.48
III	Longreach, Qld., Australia. Lat. $\approx 23.5^\circ$ S	8.8 GV	Nov. 26-27, 1969. 2224-0636 UT	2.97 ± 0.17	2.67-3.29

* Residual pressure read every 6 min to evaluate standard deviation.

0.3° , $b = +0.1 \pm 0.3^\circ$ (ref. 13), and $l = 339.8 \pm 0.15^\circ$, $b = -0.34 \pm 0.15^\circ$ (ref. 14).

We consider it exceedingly improbable that a combination of systematic errors and statistical fluctuations in the background could produce two 4σ γ -ray peaks which are at the same position as the two hardest X-ray sources in this 0.5 sr of the sky which was scanned by both the X-ray and γ -ray experiments. The combined detection of these two γ -ray emitters at known hard X-ray positions is our strongest argument for the existence of this new class of astronomical objects.

The excess above background for G γ 341+1 was found in the same way as for G γ 2+3 by comparison with the surrounding rectangle $\Delta\alpha = 28^\circ$, $\Delta \sin \delta = 0.56$. There are indications of other sources, either discrete or diffuse, within this area so the flux $F_\gamma = (1.6 \pm 0.5) \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1}$ may actually be greater. A more detailed analysis of the region around $l = 340^\circ$ will be published later. G γ 341+1 is also detectable at $E_\gamma > 500 \text{ MeV}$.

Our preliminary determination of the location of Sgr γ -1 was based on the data of flight I plus the pairs from flight II (ref. 7). We have found that a better positional determination can be made when the events used are restricted to $E_\gamma > 100 \text{ MeV}$. When this procedure is applied to Sgr γ -1 for all three flights, the mean position becomes $\alpha = 284.7 \pm 1^\circ$, $\delta = -36.9 \pm 1^\circ$. We urge that this area be searched intensively at X-ray frequencies in view of the strong correlation between G γ 2+3, G γ 341+1, and known X-ray locations.

Our preliminary data did not show the line source of γ -ray emission along the galactic plane reported by Clark, Garmire and Kraushaar¹⁷ as $4 \times 10^{-4} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ averaged over $|l| < 30^\circ$ and decreasing to one-fourth of this for $|l| > 40^\circ$. (A recalibration reduced these intensities by a factor of four¹⁸.) The experiment was done on OSO-3 with a counter telescope whose angular resolution was 15° . Kniffen and Fichtel¹⁹ found diffuse emission from the region $-39 < l < +24^\circ$, $-6 < b < +6^\circ$ with an intensity of $(2.0 \pm 0.7) \times 10^{-4} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ from a balloon-borne spark chamber.

The original OSO-3 intensity was higher by more than an order of magnitude than had been calculated for the decay of neutral pions produced in the collision of the primary cosmic radiation with interstellar hydrogen²⁰, and stimulated a search for alternative production mechanisms. Among these were

inverse Compton scattering of cosmic ray electrons by a high density (13 eV cm^{-3}) of infrared photons²¹⁻²⁵ and the superposition of point sources²⁶. Other investigators^{27,28} have concluded that π^0 production on interstellar hydrogen can explain the disk gamma rays except for the peak in the direction of the galactic centre where an additional source is required.

We have analysed our data for such a line source by taking strips parallel to the galactic equator over the region shown in Fig. 1 where the exposure was at least half of the maximum value. Events were restricted to those with zenith angle $\theta < 40^\circ$. Because the GSFC spark chamber had an HWHM acceptance angle of 13° , we also analysed those events with $\theta < 20^\circ$. The results for various flights, event types, and energy thresholds are shown in Fig. 2. Three regions will be discussed quantitatively (Table 3).

(1) H region: $-36 < l < +36^\circ$, $-2.3 < b < +2.3^\circ$. The distribution of atomic hydrogen peaks sharply along the galactic equator with an FWHM of $\approx 4-5^\circ$ (ref. 3, Fig. 1). Gamma rays from the collision of the high energy charged cosmic rays with interstellar hydrogen should follow this same spatial distribution if the cosmic ray intensity is uniform throughout the galaxy. Our angular resolution of 1.6° for a line source averaged over the atmospheric energy spectrum above 100 MeV is less than the width of the H region. The excess number of events seen above the background is 65.3 ± 31.7 and corresponds to a line intensity of $1.4 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ or a 95% confidence upper limit of $2.7 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$. The positive result can be understood entirely in terms of the discrete source G γ 341+1. When the contribution from G γ 341+1 is removed, the upper limit to the line intensity becomes $1.3 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$, a value close to that originally calculated for neutral pion production on interstellar hydrogen²⁰.

(2) GSFC region: $-40 < l < +24^\circ$, $-6 < b < +6^\circ$. We have analysed the same region¹⁹ as the GSFC flight which was made at very nearly the same location and altitude as our first two and occurred a month before flight III. If the sources G γ 341+1 and G γ 2+3 are not removed, the excess we obtain of 80.2 ± 50.1 events would yield a line intensity of $(2.4 \pm 1.5) \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$, or an upper limit of $5.3 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ (Table 3). Their removal leaves only an upper limit of $3 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ for the diffuse emission from the

Table 2 Details of the Observations

Source	Flight	$E_\gamma > 100 \text{ MeV}$; zenith angle $\theta < 40^\circ$ No. of events observed	No. of background events	α	δ	l	b	F_γ $\times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1}$
G γ 2+3	I	35	18.5	263°	-26.1°			3.1 ± 1.1
	II	46	37.1	264°	-26.1°			0.9 ± 0.7
	III	29	17.0	264°	-24.2°			1.4 ± 1.0
	Mean			$263.6 \pm 1^\circ$	$-25.4 \pm 1^\circ$	$2.0 \pm 1^\circ$	$+3.4 \pm 1^\circ$	1.5 ± 0.5
G γ 341+1	I	26	17.4	251°	-44.4°			2.0 ± 1.2
	II	51	35.4	250°	-43.6°			1.6 ± 0.8
	III	24	15.2	252°	-44.4°			1.3 ± 0.7
	Mean			$250.8 \pm 1^\circ$	$-44.0 \pm 1^\circ$	$340.9 \pm 1^\circ$	$+0.8 \pm 1^\circ$	1.6 ± 0.5
Sgr γ -1	I	33	22.1	283°	-37.6°			1.6 ± 0.8
	II	53	35.0	286°	-36.9°			1.9 ± 0.8
	III	16	10.9	284°	-35.5°			0.8 ± 0.6
	Mean			$284.7 \pm 1^\circ$	$-36.9 \pm 1^\circ$	$+0.1 \pm 1^\circ$	$-17.8 \pm 1^\circ$	1.5 ± 0.5

Table 3 Upper Limits to the Diffuse High Energy Gamma Radiation from the Galactic Centre set by this Experiment

$E_\gamma > 100 \text{ MeV}$ $\theta < 40^\circ$	N observed N predicted $I_{95}^* (\text{cm}^2 \text{ s sr})^{-1}$ $I_{95} (\text{cm}^2 \text{ s rad})^{-1}$	H region† $-36^\circ < l < 36^\circ$ $-2.3^\circ < b < 2.3^\circ$	GSFC region‡ $-40^\circ < l < 24^\circ$ $-6^\circ < b < 6^\circ$	OSO-3 region§ $-30^\circ < l < 30^\circ$ $-15^\circ < b < 15^\circ$
		928 ± 30.5 862.7 ± 8.8 3.4×10^{-4} 2.7×10^{-5}	$2,156 \pm 46.4$ $2,075.8 \pm 23.5$ 2.7×10^{-4} 5.3×10^{-5}	$5,671 \pm 75.3$ $5,813 \pm 83.3$ 9.6×10^{-5} 5.4×10^{-5}

The point sources have not been removed.

* I_{95} : 95% confidence upper limit to the γ -ray intensity. † Ref. 3. ‡ Ref. 19. § Refs. 17, 18.

GSFC region, almost an order of magnitude below the result of Kniffen and Fichtel¹⁹. It should be pointed out that thirteen discrete sources inside the GSFC region, each of intensity $1.5 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1}$ and none outside, would be required to explain their intensity of $2.0 \times 10^{-4} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$, whereas we see only two inside and one outside. The discrepancy cannot be explained by a sudden increase in intensity of one or several point sources, because the angular resolution of the Goddard chamber²⁹ is sufficient to resolve several point sources along a line over a radian long.

(3) OSO-3 region: $-30 < l < +30^\circ$, $-15 < b < +15^\circ$. Our experiment has the least sensitivity for this region because the larger solid angle includes a correspondingly larger number of background events. For $E_\gamma > 100 \text{ MeV}$ the 95% confidence upper limit is $5.4 \times 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$, a factor of two below the revised OSO-3 intensity^{17,18}. Perhaps differences in energy threshold or some other systematic uncertainty can account for this difference. Or a time dependence in the point sources may be responsible. The OSO-3 interval of γ -ray observation was finished before our flight I took place and it is entirely possible that one or several sources near the galactic centre had a cumulative flux near $1 \times 10^{-4} \gamma's \text{ cm}^{-2} \text{ s}^{-1}$ during their observation. Flaring in hard X-rays has been observed on a shorter time scale from Cen XR-2 (ref. 12). There is a slight indication that a similar change has occurred for G γ 2+3 between flights II and III (Table 2), but the statistical precision is inadequate for a definite statement.

In conclusion we have described strong evidence for the discovery of two further examples of a new type of astronomical object which emits electromagnetic radiation up to at least 10^{23} Hz , more than three decades higher than has been observed previously. In the two new cases the positions agree with known hard X-ray sources within our directional accuracy of $\pm 1^\circ$. The exponent of 2.0 ± 0.2 for the power law spectrum

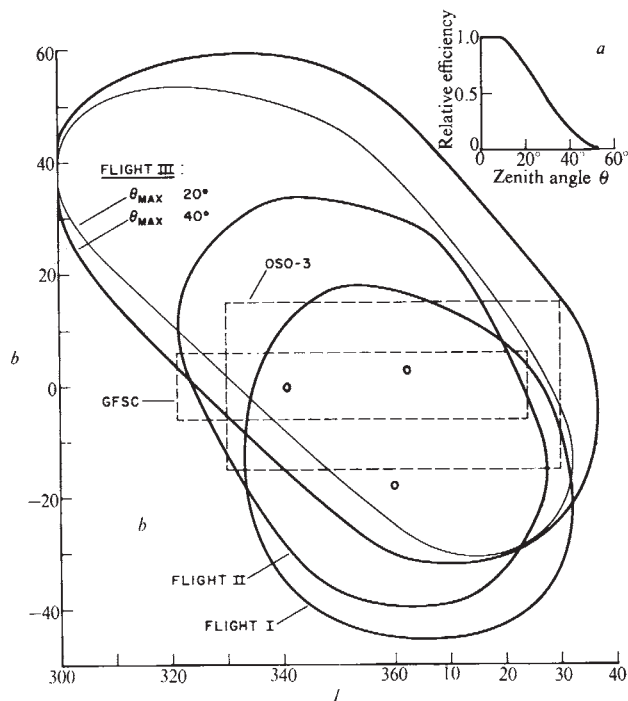


Fig. 1 *a*, The relative efficiency of the system as a function of zenith angle. The maximum ordinate corresponds to $1.03 \times 10^4 \text{ cm}^2$ of spark chamber plate area. *b*, The regions scanned on flights I, II and III. The boundaries are the contour where the exposure is 50% of the maximum value for a given flight. Events are restricted to those with zenith angle $\theta < 40^\circ$. Also shown is the 50% contour for flight III where only events with $\theta < 20^\circ$ were accepted. The two dotted regions are where an excess of γ rays was reported: OSO-3 (refs. 17, 18), GSFC (ref. 19). Open circles: point sources, this experiment.

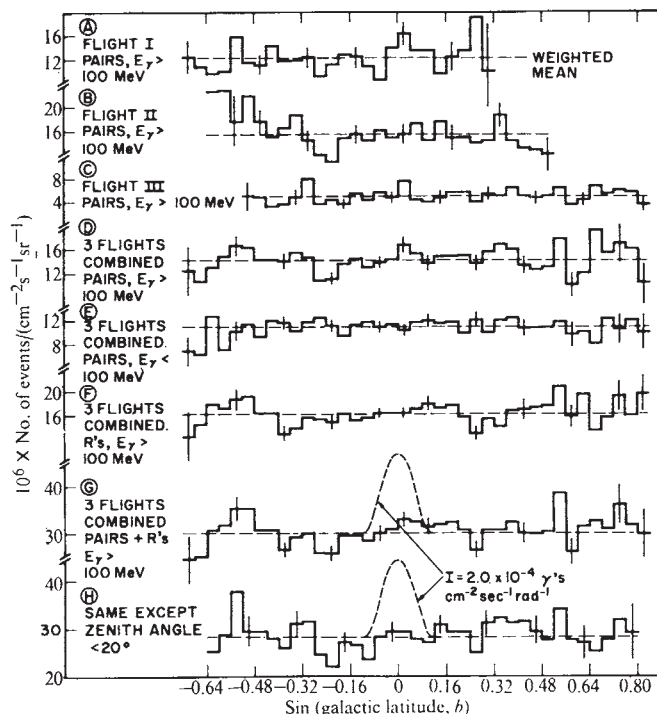


Fig. 2 Variation in γ -ray intensity scanned across the galactic equator. The limits in l for a given strip $\Delta b = 0.04$ are the 50% contours shown in Fig. 2*b*. The intensity $I_{95} = 2.0 \times 10^{-4} \text{ l's cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ was reported by Kniffen and Fichtel¹⁹.

which fits over the 20–150 keV interval also includes the 100–500 MeV point. The OSO-3 observation of the galactic centre, originally interpreted as a diffuse source, can now be considered as the combined effect of several point sources whose cumulative intensity was higher by a factor of two or three than during our flights. Whether there is still a line intensity $\sim 10^{-5} \gamma's \text{ cm}^{-2} \text{ s}^{-1} \text{ rad}^{-1}$ must be investigated in longitude regions where there are no point sources. We are in disagreement by almost an order of magnitude with the diffuse line source reported by Fichtel's group. Our upper limits eliminate the necessity for invoking inverse Compton collisions between cosmic ray electrons and infrared photons to explain the diffuse γ -ray emission from the galactic centre.

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Submillimetre Observations of the Night Sky Emission above 120 Kilometres

WE report new diffuse background measurements of the night sky obtained with three submillimetre detectors. These observations were made on December 2, 1970. A liquid-helium cooled telescope was carried by an Aerobee 170 to an altitude of 190 km. Six detectors covering bandwidths in the 5 μm –1.5 mm range were flown: the results from the near infrared detectors will be reported separately.

Previous measurements in the 0.4–1.3 mm range^{1,2} yielded the unexpectedly strong submillimetre flux of $5_{-2.5}^{+5} \times 10^{-9}$ W cm^{-2} sr^{-1} . Subsequent detector recalibration³ lowered this value to $2.5_{-1.2}^{+2.5} \times 10^{-9}$ W cm^{-2} sr^{-1} . Even with the recalibration, however, this flux corresponded to an energy density of 6.5 eV cm^{-3} , as compared with a total energy density of the 2.7 K field of 0.25 eV cm^{-3} , of which 0.17 eV cm^{-3} would fall in the 0.4–1.5 mm bandwidth. Experiments by other groups have allowed these results to be viewed in a new perspective: Muehlner and Weiss⁴, using increased spectral resolution in the same wavelength range, found that their measurements were consistent with a 2.7 K background on which a strong emission feature at 11–12 cm^{-1} is superimposed. Bortolet *et al.*⁵, from observations of interstellar absorption lines, obtained new upper limits on the intensity of background radiation at wavelengths of 1.32 mm, 0.559 mm and 0.359 mm that are all consistent with a cosmic background at 2.7 K. But these limits can only be understood in conjunction with the infrared background measurement if the intense flux is concentrated into a sharp line or lines with

$$\left(\frac{\Delta\lambda}{\lambda}\right) \leq 1/3$$

which do not overlap with the molecular resonances of CN, CH and CH⁺. The diffuse galactic gamma ray component ($E_{\gamma} \geq 100$ MeV) has been measured by several groups^{6–8}. The measurements as they now stand are not inconsistent with a large infrared background, provided that it is galactic in origin (G. P. Garmire, personal communication). An upper limit to the infrared background has been obtained by Hudson *et al.*⁹, who have measured the diffuse X-ray component from the galactic plane in the energy range 7.7–115 keV. They find an upper limit to the infrared background of 1.7×10^{-9} W cm^{-2} sr^{-1} if it is universal, assuming that the local intensity of ~ 3 GeV electrons is uniform throughout the galaxy.

The purpose of our flight was to make measurements with a more sensitive version of the 0.4–1.5 mm InSb detector in a modified payload, to verify earlier results and obtain more detailed information about the isotropy of the radiation field. In addition, a second submillimetre detector (GaAs), the bandwidth (0.2–0.45 mm) of which included the wavelength of the CH⁺ line at 0.359 mm, was flown for the first time. A third submillimetre detector, GeGa, sensitive at 0.07–0.13 mm, is useful not only because of the galactic information it can yield¹⁰, but also because it allows us to infer the magnitude of telescope heating or scattered light at the longer wavelengths. This detector measurement yields an upper limit to the submillimetre background at 100 μm .

The telescope system used was basically similar to that reported previously^{2,11}. But although the same telescope (18 cm mirror, prime focus, $f/0.9$) was used on this flight, the fields of view of the various detectors were no longer common, nor as large as before. Each detector had a separate aperture defining its own field of view of 2 square degrees.

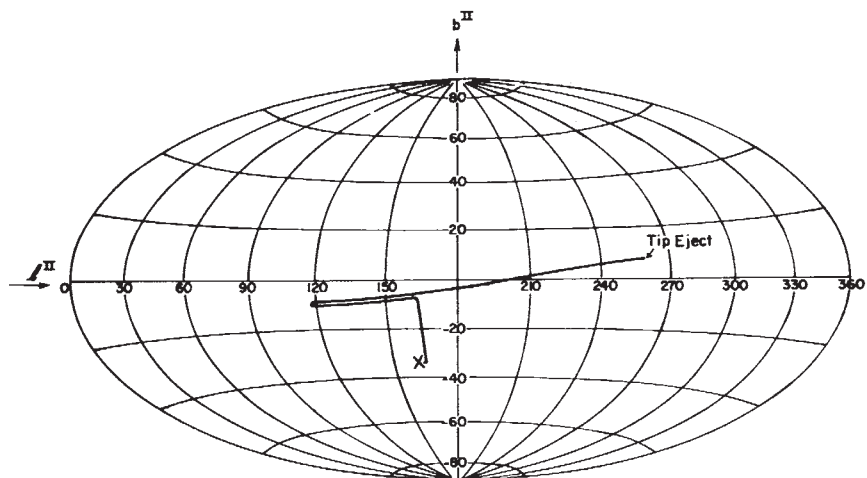
The three submillimetre detectors flown were a gallium-doped germanium (GeGa) detector, a gallium arsenide (GaAs) detector and a Rollin detector (*n*-type InSb). Both the GeGa and InSb type detectors had been flown previously, but this is the first time the submillimetre GaAs detector has been used successfully for astronomical observations. The spectral responses of the detectors and their accompanying filters were measured with a lamellar grating attachment for a Perkin-Elmer 301 far infrared spectrophotometer built by Jones *et al.*¹². The InSb detector was filtered against its intrinsic response by an interference filter and a sheet of black polyethylene, and had a long wavelength cutoff defined by two wire mesh filters. Strong atomic oxygen emission at 63 μm and 147 μm ¹³ from the upper atmosphere was rejected by the use of suitable Yoshinaga filters¹⁴ in front of the GeGa and GaAs detectors. Black polyethylene, bonded to the Yoshinaga filters, served to eliminate the intrinsic responses of these detectors.

The interior housing of the telescope was painted with a specially prepared paint, black in the infrared and suitable for cryogenic use¹⁵. Rigid cylindrical inner and outer baffles served to eliminate stray radiation; the interior surfaces of both baffles were painted black. The inner baffle, thermally coupled to the liquid helium bath, remained at 4.2 K throughout the observations, while the outer baffle stayed at 35 K. Temperature sensors on the telescope wall and the detector block confirmed that a temperature of 4.2 K persisted throughout the flight.

The system noise equivalent power (NEP) of each detector was determined in the laboratory by means of a blackbody calibration. As described before¹⁶, a 77 K blackened cavity was placed over the aperture of the telescope. The amount of flux incident on the detectors was controlled by an adjustable shutter mechanism. The NEPs measured in this way are given in Table 1.

The rocket, with the liquid helium cooled telescope, was launched at 1:32 MST on December 2, 1970. A roll-stabilized attitude control system (ACS) was used to point the telescope. The path scanned in the sky up to 227 s into the flight is shown in Fig. 1. At this time, an ACS failure occurred. The position in the sky both before and after the ACS failure was monitored by means of an aspect camera.

Fig. 1 Scan position in galactic coordinates from tip eject (nose cone and cover ejected) until the ACS failure (marked by ×).



From the time of nose cone ejection at 120 km, until peak altitude at 190 km, the payload performed normally and the data reported here were obtained during this part of the flight. The ACS failed just after peak altitude, causing the rocket to roll and cone for the rest of the flight.

The minimum signals (and the relative uncertainties) observed by the submillimetre detectors are listed in Table 1. We assign, somewhat arbitrarily, an absolute uncertainty of a factor of 1.5. Throughout this paper, the tabulated values have been used, even for upper limits. We emphasize that the absolute calibration error could change all of the intensity levels quoted by as much as a factor of 1.5.

Table 1 Characteristics of the Detectors

Detector	Spectral range (μm)	NEP ($\text{W s}^{1/2}$)	Minimum observed signals ($\text{W cm}^{-2} \text{sr}^{-1}$)
GeGa	70–130	4.5×10^{-13}	$8.5 \times 10^{-11} \pm 0.1$
GaAs	200–450	9×10^{-12}	$8 \times 10^{-11} +6 -4$
InSb	400–1,500	2×10^{-12}	$1.3 \times 10^{-9} +0.1 -0.15$

We consider the level quoted for the GaAs detector to be an upper limit, as the signal to noise ratio is of the order of one ($S/N \sim 1$). The estimate given for this detector is derived from the technique of Huber¹⁷, which allows a reasonable assessment of noisy data. The effective integration time was chosen to be 5 s, which, for the region of the sky used to evaluate the upper limit, namely the off-galactic scan, corresponds to an average over 5 degrees of sky.

The GeGa minimum signal corresponds to a relatively open area of sky, and occurs at a zenith angle of 23° . At this zenith angle, there is only a small contribution by stray radiation from the Earth, and the signal is well above the noise.

The minimum level quoted for the Rollin detector was observed both along the galactic scan ($b^{\text{II}} \approx 0^\circ$, $150^\circ \leq l^{\text{II}} \leq 210^\circ$) and off the galactic plane down to a latitude of $b^{\text{II}} = -27^\circ$. At galactic latitudes farther south than -27° , the zenith angles were larger than 35° , the angle at which the InSb detector began responding primarily to scattered earthshine. The numbers quoted are also “Huberized” averages. The errors quoted are for a 5 s average, and an average over this time scale essentially assumes the signal is uniform over five degrees.

The background signal observed by the InSb detector falls within the error of the previous recalibrated measurements, and should be considered as another confirmation of the strong infrared background. Fig. 2, a plot of the averaged data as a function of zenith angle, illustrates several interesting features about this radiation, and also shows the signal level observed just before nose cone eject. This finite level arises

because the top cover is cooled by contact with the inner baffle and after the last fill with liquid helium before the flight; the inner baffle therefore warms up slightly. Until tip eject, radiation from the slightly warm baffle reflects from the top lid into the field of view of the detectors. At tip eject, the top lid and its heat load are removed, and the temperature sensors show that the inner baffle quickly cools to 4.2 K. There is good quantitative correlation between the baffle warmup and the observed signal increase before tip eject.

The minimum signal, for both “on” and “off” galaxy data, is $1.3^{+0.1}_{-0.15} \times 10^{-9} \text{ W cm}^{-2} \text{sr}^{-1}$ for zenith angles less than 35° . The increasing flux at larger zenith angles is indicative of the detection of scattered Earth radiation. Unfortunately, the baffling function of the telescope at these wavelengths is not sufficiently well known to determine uniquely the convolution of the baffling function with the expected radiation from the Earth. Hence an unambiguous interpretation of the observed intensity between zenith angles of 37° and 52° is not possible. We can say, however, that the contribution from scattered Earth radiation for zenith angles less than 35° is small on the basis of the baffling function measurements.

The off-galaxy data cover a range of galactic latitudes from -5° to -27° at a galactic longitude of $\sim 163^\circ$, for zenith angles less than 35° . Bortolet *et al.*⁵ have pointed out that

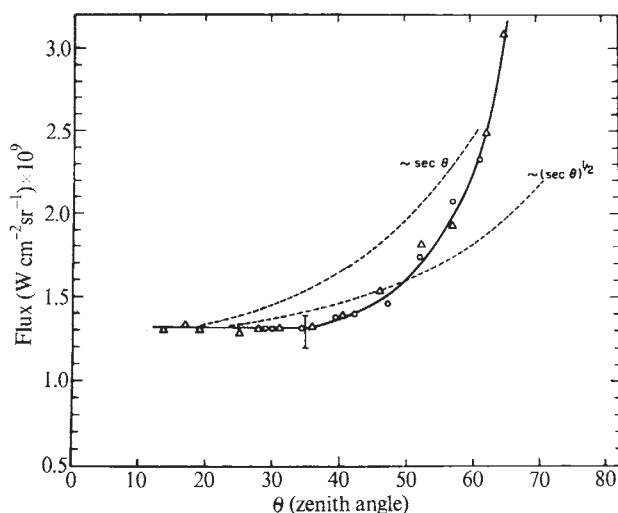


Fig. 2 Observed signal strength for the InSb detector (0.4–1.5 mm) as a function of zenith angle. The on galaxy points (Δ) refer to data from the scan along the galactic plane, while the off-galaxy points ($\circ$) refer to data from the scan perpendicular to the galactic plane. The error bar shown is typical for data in the range $10^\circ \leq \theta \leq 37^\circ$. The intensity level indicated just before the tip eject (—) was non-zero because of the reason explained in the text.

line radiation, either from the atmosphere or the galaxy, could account for the submillimetre background without producing a conflict with their measurements. Wagoner¹⁸ discussed the implications of such line radiation from our galaxy; he assumed that the line shapes are Gaussian, and that, to explain the observed isotropy of the infrared background, the optical depth is larger than unity. Under these assumptions the intensity I is given by

$$I \simeq \frac{\Sigma}{r} 4 \lambda_r^{-3} k T_e V (2 \ln \tau_r)^{1/2}$$

where $T_e (\gtrsim h\nu_r/k)$ is the excitation temperature, V is the broadening parameter, τ_r is the optical depth at the line centre ν_r , and the sum is over all resonances within the bandwidth. The optical depth at $l'' = 163^\circ$ is related to the galactic latitude b'' by

$$\tau_r(b'') \simeq \tau_r(b'' = 90^\circ) \csc(b'')$$

and so, on the assumption that the emitting material is distributed uniformly in a disk, we can estimate the optical depth by considering the observed degree of isotropy of our submillimetre flux as a function of b'' . We find for a single line in the range $-5^\circ \geq b'' \geq -27^\circ$

$$\tau_r(b'' = -90^\circ) \geq 12$$

using error bars corresponding to a 5 s average.

The observed isotropy ($\pm 10\%$ for our 5 s integrations) provides a fairly stringent lower limit on the optical depth of galactic line radiation, if it is the source of the submillimetre flux. The requirements are not impossible to satisfy within our galaxy, so that strong galactic line emission is still consistent with these latest observations.

It is interesting to note that in these off-galaxy data, no variance in the signal was noted as this detector crossed the ecliptic plane. The $\pm 10\%$ isotropy implies an upper limit to the flux from zodiacal particles of $\sim 10^{-10} \text{ W cm}^{-2} \text{ sr}^{-1}$ at 0.4–1.5 mm.

To assess the likelihood of contamination from line (or band) radiation from the upper atmosphere, we have studied the zenith angle dependence of the flux in Fig. 2 and the intensity at a given zenith angle as a function of altitude. Observations at the same zenith angle, but at altitudes of 160 and 190 km, yield identical results to within the error. The atmospheric scale height at these altitudes is ~ 25 km; we conclude from these results that the emitting material, if atmospheric, must lie primarily above 190 km. Dalgarno¹⁹ has discussed the rotation spectrum of NO, N₂O and CO, all of which emit in the bandwidth of this detector. But recent calculations by Shimazaki and Laird²⁰, extrapolated to 190 km, indicate less than 10^2 cm^{-3} of N₂O and 10^3 cm^{-3} of NO. The CO concentration is less than that of NO and N₂O. These densities preclude night sky emission of the order of $1.3 \times 10^{-9} \text{ W cm}^{-2} \text{ sr}^{-1}$ from above 190 km unless a stimulated emission mechanism is invoked. It should also be noted that a $\sec \theta$ dependence (appropriate for either a Doppler broadened or Lorentzian line shape in the weak-line limit) is excluded by the observations shown in Fig. 2. A $(\sec \theta)^{1/2}$ or slower dependence (typical of the strong-line limit) could barely satisfy the observations, in light of the ambiguity of the exact scattered Earth shine function. We do not, however, know of any emitting substance with sufficient abundances at these altitudes to explain the observed radiation.

A local origin of the signal inside the telescope seems to be ruled out on several counts. First, the temperature of the telescope interior remained at 4.2 K while the data were being collected. Second, stray multiply reflected radiation would register more strongly on both the GaAs detector and the GeGa detector. Many details of this flight differed from those of previous flights, including a more efficient rejection filter, yet all flights yield similar results, within the error, in different conditions and surveying different paths in the sky.

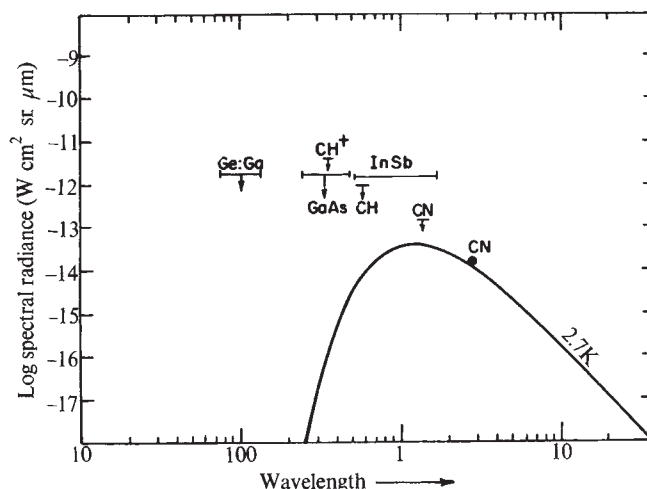


Fig. 3 A comparison of the flux from a 2.7 K blackbody with the submillimetre measurements of this experiment and the revised upper limits to the background determined from observations of interstellar absorption lines by Bortolet, Shulman and Thaddeus.

The new 0.4–1.5 mm measurement is plotted in Fig. 3 for comparison with a thermal 2.7 K background and the other submillimetre measurements.

The GaAs measurement of the submillimetre background corresponds to an upper limit of $\sim 14 \times 10^{-11} \text{ W cm}^{-2} \text{ sr}^{-1}$. A 2.7 K thermal cosmic background as inferred by the absolute radio measurements is not in conflict with this measurement or with the molecular measurements. Both this direct upper limit and the indirect molecular measurements suggest a spectral turnover for $\lambda < 1$ mm, as expected if the cosmic background is thermal. The measurement is important for another reason; if the InSb measurement were due to scattering or warming of the telescope interior, this detector would have recorded correspondingly larger signals. Because this signal is an upper limit, little information about the isotropy of the radiation can be inferred.

The minimum signal detected, $8.5 \times 10^{-11} \text{ W cm}^{-2} \text{ sr}^{-1}$, was observed at a zenith angle of 23° and at an altitude of 186 km. Because we are only interested here in establishing an upper limit to the infrared background at this wavelength, we will not discuss discrete sources of the observed flux, except to mention that the signal is at least four times larger than the expected stray radiation from the Earth (from an extrapolation of the curve measured at large zenith angles) and is unlikely to be contaminated by 63 μm radiation from atmospheric atomic oxygen, because the response at 63 μm was $\leq 0.5\%$ of that at 100 μm . The most likely source of the bulk of the signal is radiation from interstellar grains; also because the ecliptic is only 17° away from the position in the sky of the minimum signal, radiation from interplanetary grains cannot be ruled out.

In spite of these other likely sources for the 100 μm signal, the minimum observed signal stands as an upper limit to the cosmic background and is plotted on Fig. 3 for comparison with the other observations. This detector is extremely sensitive to stray Earth radiation. (A 280 K blackbody emits $\sim 10^3$ more energy in the GeGa bandwidth than in the InSb bandwidth.) If the InSb minimum signal at small zenith angles were caused by scattered earthshine, then the GeGa detector should have been saturated at $\sim 10^{-6} \text{ W cm}^{-2} \text{ sr}^{-1}$ at these zenith angles. Thus we are convinced that the strong 0.4–1.5 mm flux is not from such a cause.

This latest set of direct submillimetre observations above 120 km gives a confirmation of the background flux in the 0.4–1.5 mm band that is in excess of a 2.7 K blackbody, and upper limits to the background at 0.07–0.13 mm and 0.2–0.45 mm (Fig. 3). We feel that the measurement at 0.4–

1.5 mm indicates that the flux is not of local origin, from stray radiation, or atmospheric in nature. Lower limits to the optical depth of galactic line emission, if it is the source of this flux, have been set by the isotropy of the observed flux. Our upper limit at 0.2–0.45 mm is not in conflict with a thermal 2.7 K background or the molecular measurements. A further understanding of the submillimetre background should be gained from subsequent flights. In particular, further measurements (with increased resolution) of the isotropy of the 0.4–1.5 mm flux should indicate whether a galactic origin of the flux is most likely, or whether an extragalactic origin is indicated.

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Can the Sub-millimetre Background Radiation be Cosmological?

THE observed spectrum of the microwave background radiation¹ and the observations of interstellar absorption lines² point to a thermal origin, while the extreme isotropy of this radiation, not easily consistent with superposition of emission from discrete sources^{3–4}, suggests that the microwave background is primordial. If so, the recent observations at sub-millimetre wavelengths (Shivanandan *et al.*⁵, Houck and Harwit⁶ and Muehlner and Weiss⁷) must have a different origin. Processes before or during the recombination epoch cannot distort a primordial blackbody spectrum to the extent indicated by the sub-millimetre observations^{8,9}. If the observed isotropy⁶ of the sub-millimetre flux ($\delta I/I \leq 0.5$ within a beamwidth $\delta\Omega \sim 0.008$ steradians¹¹) is an indication of its extragalactic origin, it must have been produced at an epoch later than the recombination

epoch and probably after or during the formation of galaxies, but, in this case, it may be due to superposition of radiation from discrete sources. Another possibility is that the sub-millimetre flux is due to some optically thick resonant line in the galaxy¹⁰, or to several lines within a narrow band of frequency. Finally, a recent observation from Mauna Kea shows a background emission feature near 870 μm , consistent with ref. 7 and possibly attributable to atmospheric N_2O (I. Nolt, private communication). This observation was, however, made from a low altitude (~ 5 km), where the infrared N_2O column density is high and not well determined (M. Werner, private communication). These observations need verification.

We consider here the sub-millimetre radiation, pointing out the limitations on models which attribute this flux to extragalactic discrete sources. First, we discuss possible spectra which are consistent with the existing data and show that the filter response used for ref. 7 allows a sub-millimetre feature of significant width. Later we obtain the properties of sources required for producing this feature in two distinct cosmological models, and compare these requirements with the observed properties of various discrete sources, concluding that if the sub-millimetre background radiation is due to discrete sources, these sources have not been observed so far.

The relevant observations are the 2.7 K blackbody spectrum, the upper limits at 1.32 mm and 0.56 mm from the CN^* ($J=2$ to $J=1$ transition) and CH absorption data (here we use new upper limits reported by Thaddeus at the symposium on relativistic astrophysics in Austin, Texas, 1970); the balloon experiment⁷, with three bandpass filters; and the rocket observations^{5,6} made with a single bandpass extending from 0.4 to 1.3 mm, and a more recent rocket observation¹¹ which confirms the old results and sets new upper limits to the background radiation at 300 ± 50 μm .

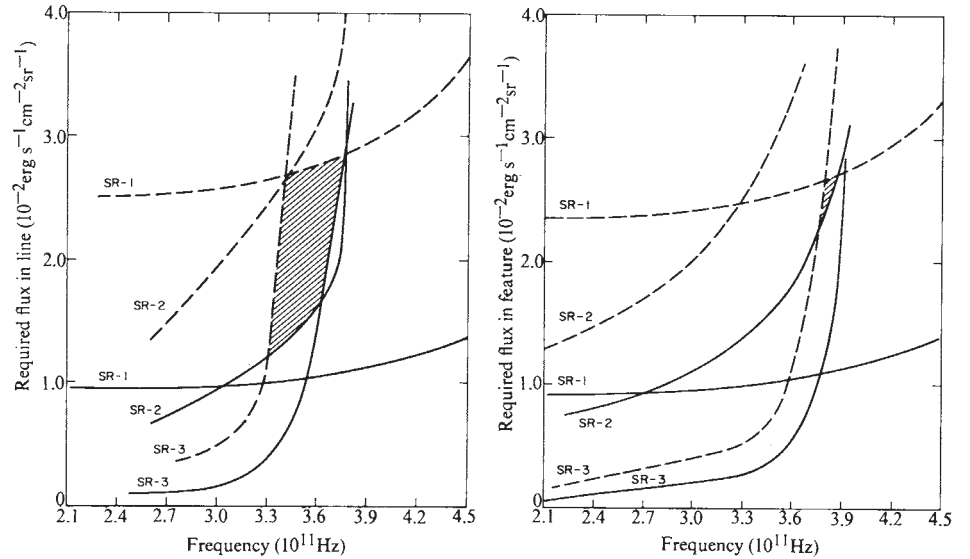
Clearly, the rocket observations are consistent with all spectra with the measured amount of flux in the given bandpass. Muehlner and Weiss indicated that their results suggest a strong line or feature centred between 0.8 and 1.0 mm. We have tested possible spectral shapes by observing the response of their filters to an assumed background flux consisting of a 2.7 K blackbody plus a feature at a wavelength $\lambda \sim 1$ mm characterized by three parameters: a total intensity, I , the peak (or central) frequency, ν_c , and the half power bandwidth $\Delta\nu$. The results were compared with the observed fluxes of ref. 7 and are shown in Fig. 1 for two spectra. In Fig. 1a the spectral feature was assumed to be a resonant line, leaving two free parameters, I and ν_c . For each ν_c and for each filter we can then calculate the value of I required to give the observed flux in that filter. The three solid lines show the curves of the required I versus ν_c for "corrected signals" (see Table 1 of ref. 7)*. Ideally, for the correct spectral shape, these three lines should intersect at a point specifying both the total intensity and the frequency ν_c . In general this will not be the case because of instrumental errors (presumably small) and uncertainties in the corrections for noise. We have assumed that the total uncertainties can be at most as large as the total corrections, leading to the dashed curves in Fig. 1a. The results then appear consistent with a resonant line feature, with

$$\begin{aligned} 3.2 \times 10^{11} \text{ Hz} < \nu_c < 3.9 \times 10^{11} \text{ Hz} \\ 1.3 \times 10^{-2} < I < 2.8 \times 10^{-2} \text{ erg s}^{-1} \text{ cm}^{-2} \text{ sr}^{-1} \end{aligned} \quad (1)$$

With such a large allowance for errors, details of the spectrum cannot be detected, and we can at most hope to specify an average spectral width $\Delta\nu$, such that the peak specific intensity $I(\nu_c) = I/\Delta\nu$. Increasing $\Delta\nu$ from zero further restricts the possible ranges of I and ν_c . The curves in Fig. 1b are drawn for a $\Delta\nu = 1.2 \times 10^{11}$ Hz, the maximum allowable width for the assumed uncertainties.

*There is an error in this table. The contribution due to atmospheric O_2 in SR-2 should read, 0.15×10^{-8} V, giving a new value of the corrected signal of 2.5×10^{-8} V. We thank Dr G. Augason for pointing this out.

Fig. 1 The flux I required to give the observed response in each filter is plotted against the central frequency ν_c of the assumed spectral feature. Solid lines refer to ref. 7's "corrected signals"; dashed lines refer to the raw signals. The shaded regions indicate where a solution is possible, consistent with all three filters. *a*, $I(\nu) = I\delta(\nu - \nu_c)$; *b*, $I(\nu) = I/\Delta\nu$, $\nu_c - \frac{\Delta\nu}{2} < \nu < \nu_c + \frac{\Delta\nu}{2}$, $I(\nu) = 0$ otherwise. $\Delta\nu = 1.2 \times 10^{11}$ Hz.



Thus, based on the work of Muehlner and Weiss, we conclude that the sub-millimetre feature must have a half power width satisfying

$$0 < \Delta\nu/\nu_c < 0.3 \quad (2)$$

The upper limit on $\Delta\nu$ will be smaller for a smaller uncertainty in the observed signal. For example, $\Delta\nu/\nu_c < 0.13$ and 0.04 if the uncertainties in the values of the various noises are, respectively, $3/4$ and $1/2$ of those assumed above. Because we are interested in the limits set on the cosmological sources by these observations we consider the most favourable case—the widest possible spectral width. Now, the spectrum of the sub-millimetre background must decrease rapidly away from ν_c to be consistent with the upper limits from molecular lines and the upper limit at $300 \mu\text{m}^{11}$. If, for simplicity, we assume a power law spectrum for $\nu > \nu_c$ and $\nu < \nu_c$, these upper limits and equation (2) imply

$$I(\nu) = K' \times (\nu/\nu_c)^{\alpha} \begin{cases} \alpha \lesssim -5, \nu > \nu_c \\ \alpha \gtrsim 6, \nu < \nu_c \end{cases} \quad (3)$$

These requirements place severe constraints on possible cosmological sources of this radiation.

If the sub-millimetre radiation is cosmological in origin and is produced by sources whose number per unit co-moving volume is n and whose luminosity is $L(\nu) = Lf(\nu)$, where $\int f(\nu)d\nu = 1$, then the background intensity per steradian due to redshifted radiation from all epochs in zero pressure general relativistic cosmological models is

$$I(\nu) = K \int_1^{\infty} f(\nu Z) G(Z) h(Z) dZ/Z$$

$$Z = 1 + z, \quad K = \frac{n_0 L_0 c}{4\pi H_0}, \quad h(Z) = \frac{n(Z)L(Z)}{n_0 L_0}$$

$$G(Z) = [2\sigma_0 Z^3 - (3\sigma_0 - q_0 - 1)Z^2 + (\sigma_0 - q_0)]^{-1/2} \quad (4)$$

Here H_0 , σ_0 and q_0 are the Hubble constant, the density, and the deceleration parameters specifying the cosmological model; subscript zero refers to the present epoch. The function h describes the evolution of the sources. The expansion of the universe spreads the radiation in wavelength, so that the observations can only be satisfied if $f(\nu)$ is more sharply peaked than the spectrum in equation (3). We shall consider the case of resonant line emission, $f(\nu) = \delta(\nu - \nu_0)$, when $I(\nu) = 0$ for $\nu > \nu_0$, while for $\nu < \nu_0$

$$I(\nu) = (K/\nu_0) G(\nu_0/\nu) h(\nu_0/\nu) \quad (5)$$

The observed background spectrum can be reproduced if most of the emission occurs within a narrow range of redshifts ΔZ around the redshift $z_c = Z_c - 1$, where from equation (2)

$$(\nu_0/\nu_0) \equiv Z_c \gtrsim 3.3\Delta Z \quad (6)$$

For cosmological models with zero cosmological constant ($\sigma_0 = q_0$), $G(Z) \propto Z^{-3/2}$ for $Z > |1 - 1/(2q_0)|$, and equation (3) can be satisfied only if the sources evolve such that

$$h(Z) = Z^{\beta}, \quad \beta \gtrsim 6.5 \text{ for } Z < Z_c$$

$$h(Z) = Z_c^{\beta} (Z/Z_c)^{\beta'}, \quad \beta' \lesssim -4.5 \text{ for } Z > Z_c \quad (7)$$

For $Z < Z_c$ this is similar to the evolution suggested by the radio source counts¹² and quasistellar sources¹³ ($Z_c \sim 3$). But recent observations of quasistellar sources with large redshifts indicate^{14,15} that β' cannot be very much smaller than zero. In Fig. 2a we have plotted various spectra for the Einstein-de Sitter cosmological model ($\sigma_0 = q_0 = 1/2$). The two solid lines are for $\beta = 6.5$ and $\beta' = -4.5$, as required by the sub-millimetre observations, and for $\beta = 6.5$ and $\beta' = 1.0$, as suggested by the redshift distribution of quasistellar sources. Clearly, the second case violates the results of ref. 7 and the observed upper limits set by the interstellar CN absorption lines.

Our spectra are all normalized by numerical integration to give the minimum possible observed flux I_1 through the widest filter of ref. 7. Spectra are chosen which satisfy equation (2), so that this normalization automatically applies to the other filters of refs. 5-7. For example, if the SR-1 filter response is a flat response with a sharp cutoff at frequency $\nu_1 \sim 5.5 \times 10^{11}$ Hz, which will provide a reasonable estimate of the transmitted flux, considering the assumed large uncertainties, we find

$$I_1 = K Z_c^{\beta-2.5} \left\{ \frac{1}{2.5-\beta'} + \frac{1}{\beta-2.5} \left[1 - \left(\frac{\nu_1}{\nu_c} \right)^{2.5-\beta} \right] \right\} \quad (8)$$

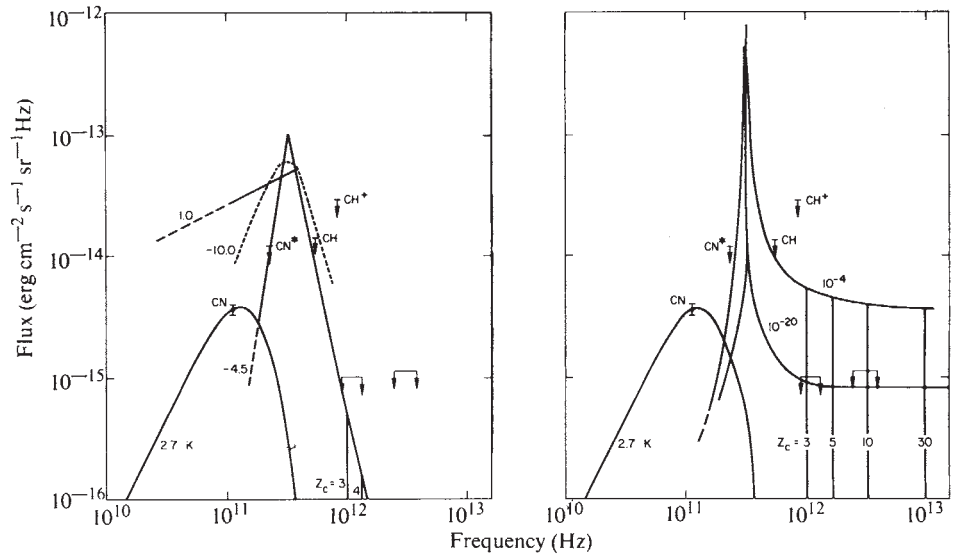
where $I_1 \approx 1.5 \times 10^{-2} \text{ erg s}^{-1} \text{ cm}^{-2} \text{ sr}^{-1}$. Using equations (4) and (7) we obtain

$$E_0 \equiv \left(\frac{n_0}{\text{Mpc}^3} \right) \left(\frac{L_0}{10^{43} \text{ erg s}^{-1}} \right) \approx Z_c^{2.5-\beta} \times 1.6 \times 10^2 \quad (9)$$

For $Z_c \approx 3.2$ and $\beta \approx 6.5$, $E_0 \approx 1$.

Another possibility for producing a sharply peaked spectrum occurs in Lemaitre-type cosmological models¹⁶, with non-zero cosmological constant λ and a long quasistatic period at redshift z_c . Strong quasar evolution is not necessary in these models¹⁷ [where $\sigma_0^{-1} = 2 - 3Z_c + \lambda Z_c^3$, $q_0 = \lambda_0(1 - \lambda Z_c^3)$], and

Fig. 2 Comparison of the expected background radiation from discrete sources with the observed values. Solid lines for a resonant line emission. Dashed line for an emitted spectrum similar to the infrared spectrum of the centre of the galaxy. *a*, Einstein-de Sitter model with evolution such that $\beta=6.5$ and with values of β' indicated on the curves (equation (7)). *b*, Lemaitre model with $\varepsilon=10^{-4}$ and 10^{-20} (no evolution) and with various values of critical redshift Z_c .



we set $h(Z)=1$ to obtain (equations (5) and (4))

$$I(\nu) = K/(Z_c v_c) \times g(1/Z_c)/g(v_c/v) \quad (10)$$

$$g(x) = (2x^3 - 3x^2 + 1 + \varepsilon)^{1/2}, \quad \varepsilon \equiv \lambda^{-1}$$

This spectrum has a maximum $v_c \equiv Z_c v_0$ of $I(v_c) \propto \varepsilon^{-1/2}$, and a full half power bandwidth $\Delta\nu = 2\sqrt{\varepsilon} v_c$. Thus, a spectral feature consistent with equation (2) is possible for $\varepsilon \leq 0.02$, when the cosmological constant is only slightly larger than the critical value required for the Einstein static model (which, in our units, is one). For $\varepsilon \ll 1$ and assuming a flat response for SR-1, we can integrate equation (10) approximately, obtaining $I(\nu > Z_c v_c = 0)$ and for $\nu < Z_c v_c$

$$I(\nu) = (I_1/v_c) \left[g\left(\frac{v_c}{\nu}\right) \left(1.0 - \frac{\ln \varepsilon}{\sqrt{3}}\right) \right]$$

$$E_0 = Z_c \times \left[g\left(\frac{1}{Z_c}\right) \left(1.0 - \frac{\ln \varepsilon}{\sqrt{3}}\right) \right]^{-1} \times 40 \quad (11)$$

In Fig. 2*b* are plotted several spectra for Lemaitre models. For given ε and different Z_c , identical spectra are obtained, but these extend to different rest frequencies $\nu_0 = v_c Z_c$. These spectra indicate that all of the observational requirements can easily be satisfied except the recent upper limits at 300 μm . Thus, for reasonable values of ε we must have $Z_c \lesssim 3$. Larger values of Z_c are possible only for $\varepsilon \lesssim 10^{-20}$.

We have discussed two possible ways of obtaining a peaked spectrum from the superposition of radiation from discrete sources, considering only the shape of the spectrum. This consideration alone requires an emitted spectrum of extremely small half power bandwidth and sets stringent limits on the source evolution in conventional cosmological models or requires a Lemaitre model of extremely long quasistatic period. The most obvious sources of the sub-millimetre background radiation are the far infrared sources discovered by Low and his collaborators¹⁸⁻²⁰. These observations indicate a flux in the 50 to 300 micron bandwidth of $10^{41} \text{ erg s}^{-1}$ from the centre of our galaxy, $10^{46} \text{ erg s}^{-1}$ from the Seyfert galaxy NGC 1068, and $10^{48} \text{ erg s}^{-1}$ from 3C 273, if its spectrum is similar to that of our galaxy. Assuming that the emission from these sources is typical, respectively, of all galaxies ($n_0 \sim 0.1 \text{ Mpc}^{-3}$), Seyfert galaxies ($n_0 \sim 10^{-3} \text{ Mpc}^{-3}$), and bright quasars ($n_0 \sim 10^{-7} \text{ Mpc}^{-3}$), then the respective values of E_0 are 10^{-3} , 1 and 0.1. (Note that the estimated local number density of all (radio active and radio quiet) quasars can be^{14,15} as high as 10^{-6} Mpc^{-3} . But this requires that all quasars, the majority of which are much weaker emitters than 3C 273, emit $10^{48} \text{ erg s}^{-1}$ in far infrared.) If all these sources evolved as the quasars ($\beta=6.5$, $Z_c=3.2$ in the $q_0=\sigma_0=1/2$ model), then only

the Seyfert galaxies²¹ could account for the observed energy in the sub-millimetre region (equation (9)).

On the other hand, many essential difficulties arise in assuming that Seyfert galaxies produce the sub-millimetre background. (i) The required source evolution with the value $\beta' < -4.5$ is in disagreement with data on quasars. (ii) If the infrared spectrum of all Seyfert's is like the spectrum of the centre of our galaxy¹⁹ the resulting background feature would be too wide. If we use the spectrum suggested by Aumann and Low¹⁹, we obtain the dashed line in Fig. 2*a* which clearly violates the observed upper limits. Furthermore, Aumann and Low give $\nu_0 \approx 4 \times 10^{12} \text{ Hz}$, corresponding to Z_c of about 11, in contrast to $Z_c \approx 3$ as indicated by quasars.

(iii) As Setti and Woltjer²¹ mentioned, the sources of the sub-millimetre radiation must be weak emitters at other wavelengths to agree with the observational constraints at those wavelengths. This difficulty can be overcome if these sources evolved such that the ratio of the infrared to other luminosities at the epoch $Z_c=3.2$ were $Z_c^{6.5} \approx 2,000$ times larger than at the present epoch.

(iv) If the strong evolution is due to an increase in source density, Seyferts, which presently constitute 1% of all galaxies, would have been twenty times more numerous than "normal" galaxies (non-evolving) at $Z_c=3.2$. Presumably, most of these earlier Seyfert galaxies have become invisible (dead) galaxies, contributing approximately $20 \times \rho_{\text{gal}} \sim 10^{-29} \text{ g cm}^{-3}$ to the present average density in the universe, where ρ_{gal} is Oort's value for the average density due to ordinary galaxies. But, if the required evolution is the result of changes in the infrared luminosity of the sources and Seyferts have always constituted only 1% of all galaxies (non-evolving), then their infrared luminosity at $Z_c=3.2$ must have been $2 \times 10^{49} \text{ erg s}^{-1}$. If the efficiency of conversion of mass into infrared photons is α , then at the epoch Z_c one galactic mass ($\sim 10^{11} M_\odot$) would have lasted for only $3\alpha \times 10^8 \text{ yr}$, an age much shorter than the Hubble time ($H_0^{-1} Z_c^{-1.5} = 2 \times 10^9 \text{ yr}$) at that epoch. This again implies many dead Seyfert galaxies. It can be shown that, in the Einstein-de Sitter model, the ratio of numbers of dead to active Seyfert galaxies is (see equation (9)) $L_0 Z_c \beta^{-1.5} [(\beta-1.5)H_0 \alpha M_{\text{gal}} c^2] \approx 0.6 Z_c / \alpha \approx 10^3$ (for $Z_c=3.2$ and $\alpha=0.002$, 30% hydrogen to helium conversion), and the present average matter density due to the dead galaxies is $\rho_0 \approx 10 \times \rho_{\text{gal}}$. In general, an efficiency $\alpha \sim 0.1$ (ρ_{gal}/ρ_0) is required if the sub-millimetre feature is produced at $Z_c \sim 3$ (ref. 22).

Lemaitre models can avoid the problems of source evolution. But for $\varepsilon \gtrsim 10^{-4}$ (a limit set by the radio background measurements if radio sources are also present during the quasistatic period²³) Z_c must be ≤ 3 , and $E_0 \approx 25$, a value much larger than indicated by the infrared observations. Only for extremely

small values of ϵ (which can be ruled out on other grounds²⁴) can the required value of E_0 be brought into agreement with the observations. Furthermore, there will be a number of dead Seyfert galaxies in Lemaitre models also. Each source must emit during the quasistatic period which lasts $t \approx H_0^{-1} g(1/Z_c)$ $[2.2 - \frac{\ln \epsilon}{3}]$ yr, thereby expending $t L_0 \sim 3 \times 10^{63}$ ergs (equation (11)) independent of the value of ϵ . Thus each galaxy must emit with an efficiency of more than 1%. For an efficiency $\alpha = 0.002$ there will be five or more dead galaxies for every active galaxy and consequently $\rho_0 \gtrsim 6\rho_{gal} \sim 2 \times 10^{-30}$ g cm⁻³. Because the present matter density in these models ($\lambda \sim 1$, $Z_c \gtrsim 3$) is $\leq 10^{-30}$ g cm⁻³, α must be larger than 0.2%.

We conclude that the observed spectrum and the upper limits set on the background radiation make it exceedingly difficult to produce the sub-millimetre feature by the superposition of radiation from cosmological sources. Furthermore, there are no known sources with the required emission characteristics and evolution. Finally, an extraordinarily efficient mechanism for conversion of rest mass into infrared photons is required, particularly for low density universes. This efficiency can only be reduced for high density universes, where most of the matter resides in dead galaxies.

We have so far considered only discrete sources. Emission by the diffuse intergalactic medium, IGM, is also a possibility. Processes involving a continuum of radiation distort the black-body spectrum but cannot produce the sub-millimetre feature. In the case of line emission by the IGM (when $n(z) < (z) = E(Z)$ is the emission rate per unit co-moving volume) rapid evolution of the IGM is required because for the more favourable case of optically thin, collisionally excited unsaturated lines ($E(z) \propto (\text{particle density})^2$) the evolutionary function $h(Z) = Z^3$, if there is no evolution of the IGM. If the IGM is optically thick and if there is population inversion the spectrum $I(\nu) \propto \tau$ will be sharply peaked since the optical depth τ increases with redshift. For the $\sigma_0 = q_0 - 1/2$ model, $\tau \propto (1+z)^{3/2}$ and $I(\nu) \propto \exp[\tau_0(\nu_0/\nu)^{3/2}]$ for $\nu < \nu_0$. In Lemaitre models the amplification due to the maser action becomes more pronounced and $I(\nu) \propto \exp[\tau_0(\nu_0/\nu)^3/g(\nu_0/\nu Z_c)]$. Although such a process can produce a narrow spectrum, the problem of the source of the energy remains.

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Neutrons in the Solar Corona

Fowler and Hashemi¹ have proposed the tempting hypothesis that neutrons constitute an energy source for the solar corona. There are, however, several important objections.

It seems very hazardous to take the upper limit of D/H on the Sun's surface to equal 4×10^{-5} . This upper limit is quoted by Kinman² who states that "there is no evidence for a deuterium line in the Sun". Deuterium is also more easily destroyed by thermonuclear protons than other light elements; for example, the solar abundance of lithium (Li/H $\sim 10^{-11}$) is a factor of about 100 less than the solar system value (Li/H $\sim 10^{-9}$ by using H/Si = 3×10^4). The Sun's surface must therefore be very poor in deuterium but, nonetheless, we shall adopt D/H = 4×10^{-5} in the following discussion.

If one considers the subsurface thermonuclear process, the reaction $D + D = n + {}^3\text{He}$ must occur near the corona, otherwise the neutrons will be rapidly thermalized and absorbed by protons. As the corona is the hottest place in the outer region of the Sun, the highest neutron production rates are obtained inside it. The number of neutrons $X_n(\text{cm}^{-3} \text{ s}^{-1})$ obtained by the reaction $D + D = n + {}^3\text{He}$ is calculated³ to be

$$X_n = 6.9 \times 10^{-16} \frac{n_D^2}{2} T_9^{-2/3} \exp \left(- \frac{4.26}{T_9^{1/3}} \right)$$

where T_9 is the temperature in units of 10^9 K and n_D the density of deuterium in particles cm⁻³.

If $T = 10^6$ K and $n_D \leq 4 \times 10^4$ deuterons cm⁻³ (ref. 4) then $X_n = 1.7 \times 10^{-24}$ neutrons cm⁻³ s⁻¹. This neutron formation rate does not explain a production of 2×10^{11} neutrons cm⁻² s⁻¹ even if the length of the solar corona is ten solar radii.

The quoted reactions $D(d,n){}^3\text{He}$, ${}^7\text{Li}(p,n){}^7\text{Be}$ and ${}^{14}\text{N}(p,n){}^{14}\text{O}$ are not the chief possibilities because the target abundances are negligible for the two first reactions and also because the (p,n) reactions do not have such large cross sections (see, for example, the unpublished report of A. A. Caretto, 1964). The principal source of neutrons is ${}^4\text{He}(p,pn){}^3\text{He}$, but even so⁵ either the neutrons produced penetrate inside the Sun or they leave the corona before their decay because the corona is too tenuous to stop them.

For all these reasons it seems difficult to believe that neutrons constitute a valuable energy source for the corona.

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Gregor's Denudation of the Continents

IN his article, "Denudation of the Continents", Gregor¹ estimated the pre-human global denudation rate at about $90\text{--}100 \times 10^{14}$ g/yr, and obtained an average rate of about 110×10^{14} g/yr for the time interval from Carboniferous to Recent. His method, however, produced a value of 400×10^{14} g/yr for pre-Carboniferous Phanerozoic time—a value he questioned seriously himself. We replotted Gregor's data on semi-logarithmic paper, converting them from volumes/yr to g/yr using his density factor of 2.6, and fitted them as simple exponential functions by drawing two straight lines; one for Carboniferous to the present, the other for late Pre-Cambrian to Devonian (Fig. 1). The dashed line, which extrapolates to a value of about 300×10^{14} g/yr, shows the reason for Gregor's 400×10^{14} g/yr as the depositional rate for these Palaeozoic and late Pre-Cambrian rocks. Such a rate would have to prevail if the rocks of Devonian and older ages have been decaying with a 120–150 m.y. half-life since their time of deposition. It seems much more likely that the Devonian and older sequence represents an interrupted cycle of deposition and destruction, for which the half-life increased markedly after the beginning of a new cycle initiated during the Carboniferous.

A test of this concept is to make a model assuming that a new cycle of erosion and deposition is starting today. The depositional rate will remain constant at 75×10^{14} g/yr. These new sediments will, like their predecessors, have a half-life of 140 m.y. The sediments now in existence, on the other hand, will not have any specified half-life, but will be drawn on in proportion to their masses to yield the sediments required for the new cycle. This is tantamount to reducing their vulnerability to erosion. The total mass of sedimentary rocks will remain constant at $32,000 \times 10^{20}$ g, an estimate taken from Garrels and Mackenzie². For convenience, the interval from Carboniferous to the present will be referred to as the Mesozoic–Caenozoic cycle; that from late Pre-Cambrian to Carboniferous as the Palaeozoic cycle.

Fig. 2 shows the results of the model calculation. Three hundred and fifty million years in the future, the relation of "New Era" sedimentary masses to Mesozoic–Caenozoic masses could be almost identical to the present day relation of Mesozoic–Caenozoic masses to Palaeozoic masses. Hence the model, although not necessarily unique, explains Gregor's mass–age relations for the Phanerozoic on the basis of changes in the probability of destruction of sedimentary rocks as a function of their ages.

Consequently, Gregor's depositional rate for the Mesozoic–Caenozoic cycle is equally applicable to the Palaeozoic cycle. If anything, the rate of deposition during the Palaeozoic may have been slightly less. The high rate he calculated and questioned can be attributed to the ending of a cycle between

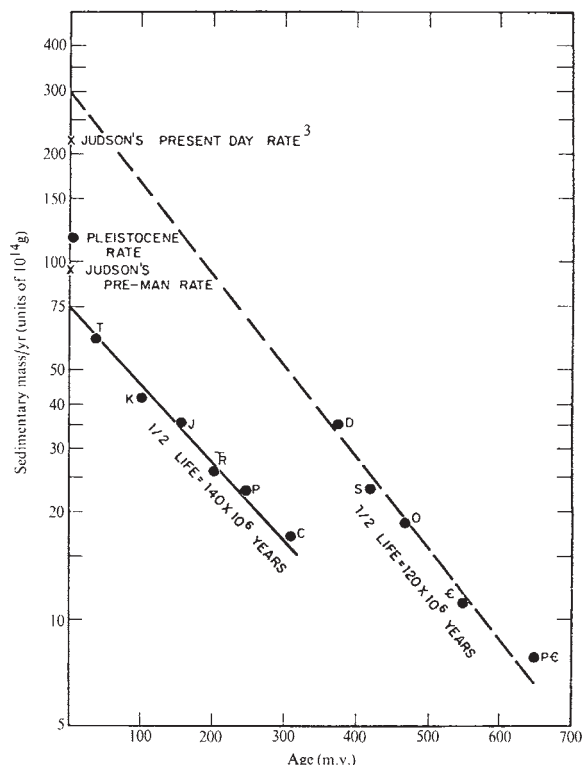
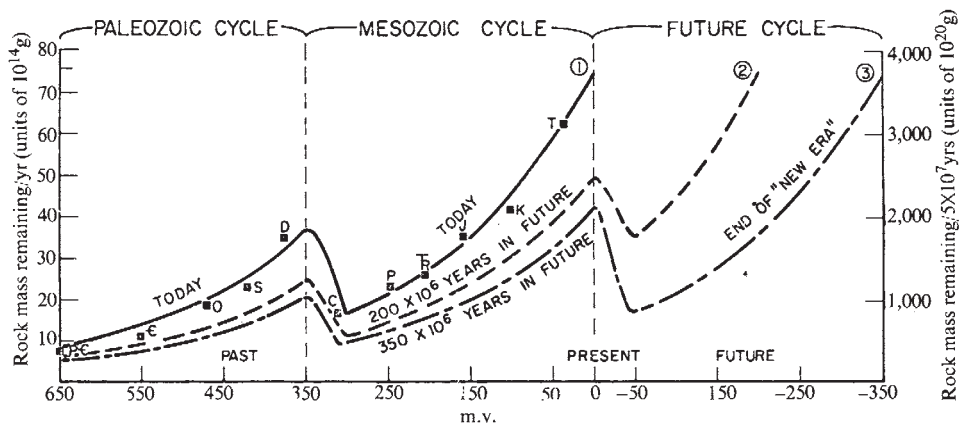


Fig. 1 Gregor's data on "mass of sedimentary rocks remaining per unit of time" plotted semilogarithmically to illustrate that the distribution of sedimentary mass can be regarded as two independent decay schemes with approximately the same half-life for the interval from late Pre-Cambrian to Carboniferous as for that from Carboniferous to the present.

Devonian and Carboniferous time, after which the rate of destruction of Devonian and older sediments decreased markedly. Gregor's model assumed equal probability of destruction for all rocks, independent of their age. In our interpretation of his data, two sedimentary cycles have occurred since the late Pre-Cambrian, and the half-life of the rocks, during their cycles, has been approximately 140×10^6 yr. After the end of a cycle, the half-life of the rocks of the older cycle increases steadily as the new cycle progresses, rising to 600 or 700 m.y. some 350 m.y. after the beginning of a new cycle. The overall half-life or "half-mass age" of all sedimentary rocks, according to the model used, is about 430 m.y. Stated otherwise, it would take 430 m.y. to deposit a mass of sediments equal to the total mass in existence today. Depositional rate and the sedimentary mass may well have remained nearly constant.

Many tectonic models can be made that fit the cycle concept; one is of a cycle starting with extensive deposition on

Fig. 2 Graph showing the result of a predictive model calculation of the distribution of sedimentary mass remaining per unit of time for the next 350 m.y.



continental margins, shelves, and adjacent sea floor, followed by a continuous rise and relative movement of the continental block toward the area of initial deposition, culminating in folding, overriding and incorporation of the sediments into the continental mass. During the early rise of the continental mass, early deposited gently dipping sediments are rapidly stripped; the final tectonism protects the remainder of the sediments by infolding them with older continental material, so that they are no longer selectively destroyed. It is tempting but perhaps premature to relate these cycles to current hypotheses of sea floor spreading and plate tectonics.

In conclusion, we wish to make it clear that our discussion rests on Gregor's numbers for the mass-age distribution of existing sediments. On the other hand, the concept of changes in the probability of destruction of sediments as the fundamental reason for major variations in the mass per year preserved today seems generally applicable. Changes in depositional rates with time, although surely important, seem to be secondary to increase or decrease in the probability of destruction in controlling the rock record available to us today. Relatively small fluctuation of erosional rate, when considered in time intervals as long as Periods, does not seem unexpected, if continental area, solar energy, and the Earth's internal energy have remained about the same.

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Sea Bottom Velocity Profiles on the Continental Shelf south-west of England

THE peak velocity of tidal currents on the Continental Shelf around the British Isles varies greatly from place to place, nowhere more markedly than in the south-west (Fig. 1). In this area the grade of the superficial sediment and the geometry of the sea floor are both highly variable^{1,2} and grain size tends to decrease as tidal current strength weakens^{1,3} along certain sediment transport paths¹. It is usually considered⁴⁻⁶ that the bulk of this sediment can be redistributed by tidal currents only when they are augmented by storm-induced oscillatory water movement. But it is still thought that the regular, essentially horizontal and reversing, mass water movements associated with tidal flow exert the principal, long term control on the areal distribution of sediment. We are interested in quantifying this dependency, and hope to show whether any relationship connects the median sediment grade Md and the peak horizontal shear stress $\tau_{0\max}$ exerted by tidal flow at the sediment/water interface.

At the present time there is very little hydraulic data concerning the sediment/water boundary-layer in the area and no systematic sediment sampling programme has previously been carried out there. We have collected sediment samples on a regular grid of 5' latitude $\times$ 7.5' longitude, and a representative portion of each sample has been graded using the Bristol Fall

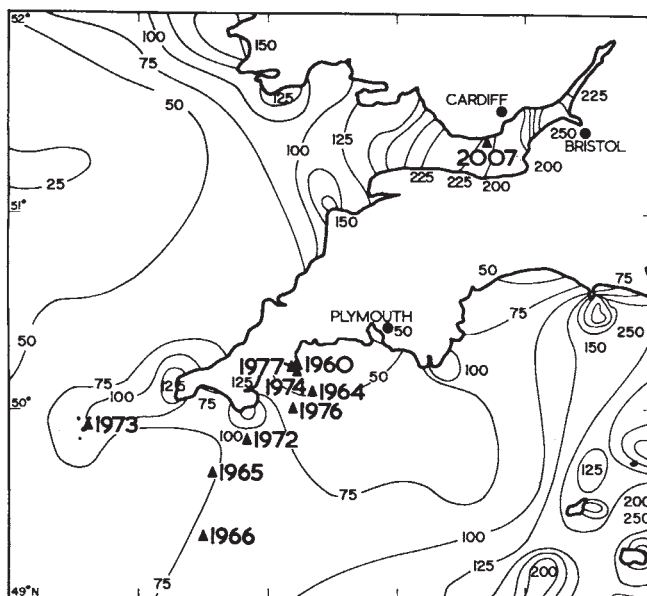


Fig. 1 Locations of boundary layer velocity profile measurements. Distribution of maximum surface current speeds—springs—are given in cm s^{-1} , adapted from Sager¹³.

Column⁷. Maps showing the areal trend of sediment size, sorting, skewness and so on have been compiled. In the same way we also intend to map the maximum horizontal shear stress that can result from peak tidal current flows at the sea bed. The horizontal shear stress acting at a given point on the sea floor depends on the local bed roughness (the roughness length Z_0 of equation (1) below). Hence the construction of a map showing maximum stress requires measurements of horizontal stress for the ranges of bed forms that occur within the area, as well as measurements of grain size and current strength.

Here we present boundary-layer observations from ten locations south-west of England. Locations and times of recordings (Fig. 1, Table 1) were chosen so that most depths and current speeds occurring in the area were represented, at various states of the tide. We regard the results as a guide only to the extremes of flow conditions that might be encountered in the area, and preliminary to systematic observations throughout the area.

The turbulent boundary layer found near the sediment water interface may be described hydrodynamically in one of three ways. (1) Smooth—the thickness of laminar sublayer δ is equal to, or greater than, the inherent roughness k of the bed; viscous forces predominate. (2) Transitional—viscous and inertial forces act. (3) Rough—at high velocities, $\delta \ll k$, roughness elements exert considerable form resistance to the flow; inertial forces predominate.

The Kármán-Prandtl boundary layer equation, as derived in Sverdrup *et al.*⁸, relates the mean current speed $\bar{U}_z$ to the height z of the observation point from the sediment/water interface. It holds true for any turbulent boundary layer, and may be written

$$\frac{\bar{U}_z}{\bar{U}_*} = 5.75 \log_{10} \frac{z}{Z_0}, \text{ where } Z_0 \ll z \quad (1)$$

Z_0 describes the effect of sea bed geometry and sediment grain size, shape, on the flow. The mean drag velocity $\bar{U}_*$ is defined as $\bar{U}_* = \sqrt{(\bar{\tau}_0/\rho)}$, where ρ is the fluid density. Several previous authors⁹⁻¹² have confirmed that the Kármán-Prandtl equation normally holds true for a turbulent sediment/water boundary layer, though most measurements have been made at shallower depths and higher Reynolds numbers than are common at this boundary layer on the eastern Atlantic Shelf.

Table 1 Boundary Layer Data (Mean Values Shown)

Location		State of tide (approximate mean)	Period of measure- ment (min)	Speed 1 m from sea floor $\bar{U}_{100}$ (cm s ⁻¹)	Corre- sponding Reynolds No. $\bar{R}_{100}$ ($\times 10^{-4}$)	Boundary shear stress $\bar{\tau}_0$ (dyn cm ⁻²)	Drag co- efficient $\bar{C}_{100}$ ($\times 10^3$)	Roughness length Z_0 (cm)	Nature of turbulent boundary flow	Comment
Station No.	Depth (m)									
Near spring tides										
SB 1960-1	29	Near slack water	20	< 6	< 4	—	—	—	—	Non-logarithmic profile
-2	29	3 h before peak ebb current	20	19.7	14.1	3.32	6.29	1.6	Transitional to rough	—
SB 1964	75	Peak ebb current	20	21.3	15.2	5.47	11.8	2.5	Rough	—
SB 1965	93	1 h after peak flood current	15	17.2	12.3	—	—	About 7	Rough	Simplified formula not applicable $Z_0 < / < Z$
SB 1966	104	3 h before peak flood current	20	28.9	20.7	2.17	2.51	0.033	Rough	—
Between spring and neap tides										
SB 1972	91	2½ h before peak ebb current	35	2.67	2.10	—	—	About 13	Transitional	Simplified formula not applicable $Z_0 < / < Z$
Near neap tides										
SB 1973-1	14	2½ h after peak flood current	20	4.94	3.89	0.148	5.89	0.53	Transitional	—
-2	14	3 h before peak ebb current	95	< 2	< 1.5	—	—	—	—	Non-logarithmic profile
-3	14	2 h before peak ebb current	20	1.56	1.23	0.00380	1.52	< 10 ⁻²	Almost smooth	—
-4	14	1 h before peak ebb current	40	2.88	2.26	0.0546	6.46	0.70	Transitional	—
-5	14	Peak ebb current	75	6.44	5.07	0.0193	0.471	< 10 ⁻⁶	—	—
Neap tides										
SB 1974	64	2 h after peak flood current	55	14.9	11.5	1.22	5.39	0.44	Transitional to rough	—
SB 1976	75	Near slack water	50	About 7.5	About 5.8	—	—	—	—	Scattered data values
Neap tides										
SB 1977	26	Peak flood current	100	< 1	< 0.75	—	—	—	—	Non-logarithmic profile. Area of low peak current speeds
JMB 2007	22	Between spring and neap tides. Peak ebb current	30	96.5	76.6	63.7	6.67	0.75	Rough	—

Conforming to previous practice, we have taken simultaneous current speed recordings at several heights within the boundary layer, using current speed transducers mounted inside a weighted frame on the sea bed. The Bristol velocity gradient unit has five propeller-type transducers measuring at logarithmically spaced heights up to 2 m from the sea bed. Propeller revolutions were integrated over 5 min periods to provide current speed recordings, but for simplicity Table 1 shows results averaged over longer periods of near constant Reynolds number $\bar{Re}_{100}$. $\bar{U}_*$ and Z_0 have been obtained from the slopes and intercepts, respectively, of straight line plots of $\bar{U}_z$ against $\log z$. The velocity at 1 m from the sea floor ($\bar{U}_{100}$) and its corresponding Reynolds number ($\bar{Re}_{100}$) are also shown in Table 1, together with $\bar{\tau}_0$, Z_0 and the mean drag coefficient $\bar{C}_{100}$. $\bar{C}_{100}$ is derived from the quadratic stress law—

$$\tau_0 = C_z \cdot \rho \cdot U_*^2 \quad (2)$$

which may be used more readily in the form $\bar{C}_{100} = \bar{U}_*^2 / \bar{U}_{100}^2$,

since $\bar{U}_* = \sqrt{(\bar{\tau}_0/\rho)}$. For smooth flow $Z_0 = \frac{0.11 \nu}{\bar{U}_*}$, where ν is the

kinematic viscosity of the fluid, and the drag coefficient $\bar{C}_{100}$ is an exact function of $\bar{U}_*$, z and ν . The dispersion of $\bar{C}_{100}$ decreases significantly as Reynolds number increases through the transitional flow regime¹¹, and for fully rough flow both $\bar{C}_{100}$ and Z_0 have a constant value dependent only on the bed geometry. A further test for the hydrodynamic nature of the boundary flow was Nikuradse's roughness criterion, used in the form given by Sternberg¹¹.

Our results confirm the Kármán-Prandtl laws except during very low velocity periods of tidal reversal. This implies an appreciable phase lag of bottom current fluctuations behind those occurring nearer the sea surface. It seems that the turbulent boundary layer flow on the shelf south-west of England is usually hydrodynamically transitional to rough. Rough flow predominates during the periods of high Reynolds number that are thought to control the sediment distribution. Sternberg¹¹ demonstrated qualitatively that the boundary between transitional and rough flow is related to the geometry of the sea bed, with complex beds such as sand waves becoming fully rough at higher Reynolds numbers than simpler patterns. Reynolds numbers $\bar{Re}_{100}$ associated with mean flow one metre from the sea bed rarely exceed 50×10^4 , except in the high velocity areas of the Bristol Channel. Approximate near-surface tidal current predictions are available on Admiralty Chart 2649 for points about 10 km from stations SB 1965 and SB 1966, and on Chart 1152 for the exact position of station JMB 2007. The predicted speeds at the times of boundary layer recordings are about 50, 40 and 170 cm s⁻¹ respectively. For stations SB 1965 and SB 1966 these near-surface speeds are approximately twice the corresponding speeds 1 m from the sea floor; the near-surface prediction for the shallower station JMB 2007 is a little less than twice $\bar{U}_{100}$, as would be expected. It seems that the boundary shear stress $\bar{\tau}_0$ associated with these bottom flows is usually less than 10 dynes cm⁻² for the area seaward from the Bristol Channel. The range of roughness length so far encountered—up to 7 cm—is in agreement with the known occurrence of high amplitude bed forms in the area^{1,2}.

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BIOLOGICAL SCIENCES

X Chromosome Inactivation studied by Injection of a Single Cell into the Mouse Blastocyst

CHIMAERISM in mice, whether naturally or artificially caused, is a valuable tool in the study of development. Much information has already been gained from chimaeras made by fusing eggs at cleavage stages¹⁻³. Chimaeras can also be made by the injection of cells into the mouse blastocyst⁴. Because this method gives chimaerism at a later stage of development it potentially yields different information⁵, and refinement of the technique to inject a single cell into each blastocyst further enhances its scope. The injected cell divides to form a single-cell clone, which can be traced through development. In the past cloning has been used for studying X chromosome inactivation in cultured cells; we have used this new method of single cell injection for studying X inactivation in the embryo *in vivo*. This communication reports the birth of several mice made chimaeric by the injection of a single cell into the blastocyst, and presents preliminary results concerning the time of X chromosome inactivation in the mouse embryo.

Coat colour markers were used as indicators of X chromosome activity. Gene combinations were so arranged that a female donor cell would, after X chromosome inactivation⁶, give either wild type or white patches in the chimaeric offspring. The host blastocyst carried autosomal genes for a third, distinguishable colour. If X inactivation had already occurred before cell transfer, the resulting chimaeric mouse would show only one of the two coat colours determined by the relevant genes of the donor cell whereas, if it occurred after transfer, patches of both donor colours should be found in the chimaera. The blastocysts which provided donor cells were obtained from albino (XX cc) females mated to males carrying Cattanach's⁷ translocation (X^T) and either cc^e or c^ec^e. From this cross all female offspring should have a coat flecked with wild type and white patches (X^TX cc^e or cc) and all sons should be white only (XY cc^e or cc). The host blastocysts were from PT females (pc^{ch}/pc^{ch}) mated to p+/p+ males, from which cross all offspring should be sandy coloured with pink eyes (p+/pc^{ch}).

Donor blastocysts were flushed from the uterus of females killed 3.5 days after mating into a medium of M199 supplemented with serum⁸. Using a Leitz micromanipulator inner cell masses were dissected from the overlying trophoblast and disaggregated in trypsin solution⁹. Host blastocysts at the same stage were placed in individual microdrops and a single disaggregated cell from a donor blastocyst was injected into the blastocoele of each. The treated blastocysts were incubated at 37° C for 1-2 h to encourage incorporation of the donor cell, and then injected into the uterine horns of anaesthetized parous recipient females mated 2 days earlier with sterile males (strain T145H). Usually five blastocysts were injected into each uterine horn, either one or both horns being used.

Among the thirty-two young which survived to weaning there were nine overt chimaeras (Table 1). The proportion of chimaeric young obtained by this technique (28%) thus

Fig. 1 Chimaeras with (A) wild type (dark) and sandy patches; (B) sandy and white patches; and (C) wild type, sandy and white patches.



compares favourably with that obtained by egg fusion². Study of the colours and coat patterns of the nine animals obtained so far (Table 2 and Fig. 1) has yielded preliminary information on *X* chromosome inactivation and development of pigment cells.

Table 1 Offspring obtained after Transfer of Blastocysts injected with Single Cells

	No. of females	Blastocysts transferred	Young born	Young weaned			
				Self colour		Chimaeric	
				♀	♂	♀	♂
Unilateral transfers *	5	28	21	9	3	3	4
Bilateral transfers	2	16	13	5	6	1	1
Total	7	44	34	14	9	4	5

* A further forty blastocysts were transferred unilaterally to eight females which did not become pregnant.

Table 2 Phenotypes of Chimaeras

	Donor colours present *		
	Wild type only	Wild type and white	White only
Female	—	3	1
Male	1	1	3
Total	1	4	4

* All animals had some patches of host colour (sandy).

The donor cell colours, white or wild type (dark), were distributed widely over the body (Fig. 1). Thus if it contributes at all to the pigmentary system, a single inner cell mass cell at the 3.5 day stage can leave descendants in many regions of the body. This is in agreement with Mintz's views that the clones of cells of which the pigmentary system of the adult is composed are formed later than 3.5 days¹⁰. Fig. 1 also shows that, in some of the chimaeras, much of the pigmentary system was derived from the donor cell. Further work is needed to distinguish between the various possible explanations of this phenomenon. For example, the donor cell may have outgrown the host cells, either because it was genetically superior, or because it was favoured by its position in the embryo. Alternatively, embryonic determination or division of function among inner cell mass cells might have occurred, so that, if the injected cell was potent to form pigment cells at all, it was one of only a few cells with such potency and consequently formed a large part of the pigmentary system.

Information about *X* chromosome inactivation is derived from the particular colours present (Table 2). Five chimaeras

had some wild type colour and therefore presumptively received a donor cell from a female blastocyst. Four of these five also had some white as well as the sandy colour of the host blastocyst. Our interpretation for this is that *X* chromosome inactivation had not yet occurred in the donor cell at the time it was transferred. When it did occur some cells had the *X*^T, carrying the wild type coat colour gene, active and others the normal *X*, so giving a white patch. We cannot exclude other explanations, such as that inactivation had occurred before transfer but was reversed by the treatment, but for the present we prefer to accept the simpler explanation as a basis for further work. The fifth chimaera had wild type and sandy patches only. For this the two following explanations are most likely. Inactivation may already have occurred before the cell was transferred, or it may have occurred within one or two cell divisions afterwards and, by chance, all of the small number of descendant cells present had the *X*^T active.

Similar explanations could be put forward for one of the four remaining chimaeras, which had no wild type but only white patches. In this case the *X*^T would be presumed to be inactive. Alternatively, the animal may have received a male cell, as progeny tests have indeed shown to be the case for the other three of these chimaeras.

These preliminary results therefore suggest that in the mouse embryo *X* chromosome inactivation is either beginning to occur in the 3.5 day blastocyst, or occurs within a few cell divisions later. Further work will be directed to testing this point.

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Chromosome Analysis of Abnormal Cells

THE karyotype of a somatic cell is the pattern obtained by the arrangement of the chromosomes into various groups by length and centromere position. The average forms of all chromosomes of a complement are defined by an idiogram, based on a large number of karyotypes. The human diploid idiogram was standardized at the Denver¹ and London² conferences on human chromosomes. By comparing normal or near normal karyotypes with the standard, it is possible without any supporting genetic data to identify changes in chromosome structure. When the cells have been taken directly from the diploid organism or when they have been in culture for only a short time, it is legitimate to ignore the numerous small shape differences, such as variations in coiling or artefacts, from the Denver-London idiogram. But when a cell population is known to be distantly descended from the parent diploid—for example, when it has been long in culture—and if the chromosome complement has changed both numerically and structurally, then comparison with the diploid idiogram is more difficult. Changes in chromosome structure are likely to have been numerous, and shape alone is not a valid criterion for chromosome identification.

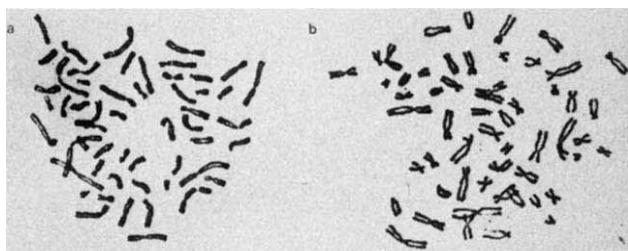


Fig. 1 Metaphase preparations of a pair of sister cells.

The force of these, perhaps obvious, considerations has been emphasized by some work on the HeLa cell line. The chromosome number variation in HeLa is well known, though there has been little study of the detailed karyotypes of the various modal cells found in different laboratories. In one HeLa line, an uncloned line⁴ obtained from the John Innes Research Institute in 1963, 40% of the cells have a chromosome mode of 55; this is the lowest mode yet reported for HeLa. Ninety-seven of these modal cells were karyotyped according to the Denver-London system. The cells were from both monolayer and suspension cultures, and experiments showed that the different methods of culturing did not affect the chromosome number distribution⁴. Cells grown in monolayer were treated with EDTA before chromosome preparations were made. Each of

the ninety-seven cells seemed to have a different karyotype. Taken at its face value, this result was difficult to accept because it suggested either that there was a very large number of sublines within the population, all with a mode of fifty-five chromosomes, none being seen twice, or that changes of karyotype were occurring so rapidly that there was only a very small likelihood of seeing two cells with exactly the same fifty-five chromosomes. But with an observed frequency of aberrant mitoses of 25% (those mitoses which could in any way give rise to changes in karyotype), this possibility is implausible unless the unlikely assumption is made that all the karyotypes produced were equally viable.

It seems therefore that this method of chromosome analysis is inadequate, and so I have tried to match the chromosome complements of pairs of sister cells, in which the chromosomes were only separated by one interphase. Sister cell metaphases were obtained by growing cells on coverslips and adding colcemid after 48 h so that the second batch of metaphases was arrested. Preparations were made *in situ* without any EDTA treatment. When two metaphases arose next to each other from sparsely sown cells, they were assumed to be sisters. The chromosomes of twenty-eight pairs of sister metaphases were counted (Fig. 1); thirteen pairs had fifty-five chromosomes in each cell. Five of these pairs were analysed by the Denver-London system which, as before, yielded different karyotypes for all ten cells (Fig. 2). The chromosomes of one cell of each of the pairs were then matched with those of its sister cell, and it was found possible to complete this quite satisfactorily for all five cell pairs (Fig. 3). A further seven pairs of sister cells, all with fifty-five chromosomes per cell, were successfully matched in the same way. The twelve sister cell pairs analysed were chosen because they had the stemline chromosome number of the population. The figure of 25% aberrant mitoses mentioned here refers to the whole population and therefore does not apply to the twelve selected cell pairs; there were also sister cell pairs that did not have the stemline chromosome number.

These results, in contrast with the earlier result, indicate that the chromosome complements within each sister cell pair are identical. A more detailed inspection of the karyotypes showed that each cell of the twelve pairs had thirty-eight metacentric/submetacentric and seventeen acrocentric/telocentric chromosomes (Fig. 3). In the latter group there were always two large acrocentrics and a satellited acrocentric which was usually the fourth from smallest.

Four of the original ninety-seven cells analysed earlier were then re-examined and were also found to conform to this description, although they had been judged to be different from each other when compared by way of the Denver-London system. It seems very unlikely that these constant karyotypic features would appear undisturbed if the chromosome complement of the modal population was continually changing, and it is probable that the complements of all the twelve sister cell pairs are identical.



Fig. 2 Karyotypes of the same pair of sister cells according to the Denver-London system, showing many apparent differences between them.



Fig. 3 Chromosomes of the same pair of sister cells showing how chromosomes from one cell can be matched with those from the other. The two groups of thirty-eight metacentric/sub-metacentric and seventeen acrocentric/teolocentric chromosomes are clear.

It is concluded that the karyotypes of cells from long established human lines such as HeLa are best compared by matching with one another rather than by indirect comparison through the remotely related Denver-London idiogram. As already explained, their relationship with the idiogram is so distant that there are overwhelming general objections to such a comparison, and the present example shows how misleading the comparison may be in practice.

It seems probable that some of the results of Hughes⁵ were prejudiced by such errors. Hughes made use of some of the HeLa karyotype data which I have included here, based on the comparison with the Denver-London idiogram, to support his conclusion that HeLa modal cells have very diverse chromosome complements. Furthermore, it should be noted that he reached the same conclusion with three Burkitt lymphoma lines (EB1, EB2 and EB3 (refs. 6 and 7)), although here again the karyotypes were compared through the Denver-London system. These observations must be suspect, especially since Hughes⁵ himself reports that the chromosome aberration frequency at mitosis in the Burkitt lines was "too low . . . to account for the great diversity of karyotypes", and therefore agrees with the present HeLa result. His observations should not be taken as evidence for cross-support between cells in culture.

It is unreliable to compare highly abnormal karyotypes with a diploid idiogram. Clearly, conclusions drawn from such comparisons^{3,5,8} should be re-evaluated.

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Identification of an Unusual Y Chromosome in YY Mosaicism by Quinacrine Fluorescence

We have recently had the opportunity to study the rare association of mixed gonadal dysgenesis in a female child and $X/XY/XXX$ mosaicism in karyotypes from blood and fibroblast cultures. The quinacrine fluorescence technique^{1,2} permitted us to identify the Y chromosome, which in this case is unusually large and not identifiable for certain by other means. So far the value of the quinacrine fluorescence technique has been primarily in screening for extra Y chromosomes and for karyotyping. Now it seems that this new technique may supplant or substitute autoradiographic analysis³.

Table 1 Chromosome Studies of Proposita

Proposita	Karyotypes (%)			Total No. of cells
	45, X	46, XY	47, XYY	
Blood	0	75	25	100
Skin	34	18	48	50
Right streak	47	50	3	100
Left gonad	68	28	4	50

About 6% of the cells showed random loss of one chromosome.

Our patient, a 5 yr old Caucasian girl, had the primary features of enlarged clitoris, obesity, normal stature and normal intelligence. Sex chromatin from buccal smears was negative (600 cells examined). Two cell lines of 46, XY/47, XYY? were found in chromosome analyses from blood, and three cell lines in analyses from fibroblast culture, 45, X/46, XY?/47, XYY?. Chromosome studies of the proposita are in Table 1. The chromosome which we tentatively identified as a Y was as large as a chromosome of the D group, and in most preparations had the morphological characteristics of a Y chromosome—parallel long arms and no satellites (Fig. 1). Secondary constriction of the long arms, frequently observed in Y chromosomes, was not an outstanding feature. Autoradiography showed heavy labelling, which is consistent with the

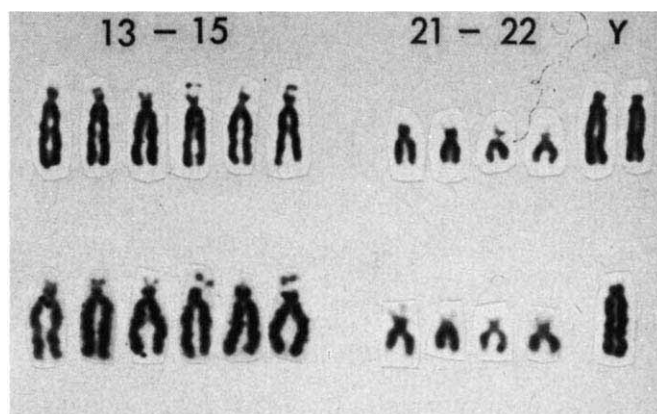


Fig. 1 D group, G group and Y chromosomes from two cells of the proposita (peripheral blood culture). The top row of chromosomes is from a 47, XYY cell line; the bottom row from a 46, XY cell line. The Y chromosomes are morphologically distinguishable from the D chromosomes in these preparations.

pattern of either a late labelling, partially deleted *X* chromosome (*Xp*-) or a *Y* chromosome. It is impossible to compare the presumptive *Y* of the child with that of the father who is not available for study. Karyotype of the mother was apparently normal female, 46, XX.

Quinacrine (quinacrine hydrochloride) fluorescence of interphase nuclei from the fibroblast culture showed one or two brightly fluorescing regions in some cells (Fig. 2), which are consistent with the *Y* body⁴. Quinacrine labelling of metaphases showed a brightly fluorescing band on the long arm of the *Y* chromosome, which is also consistent with descriptions of *Y* fluorescence³. The brightly fluorescing area on the *Y* chromosome starts at the expected distance from the centromere but unexpectedly does not extend throughout the entire length of the long arm (Fig. 3). We suggest two alternative explanations for this unusual fluorescence pattern. A *Y* chromosome of this length, which is recognized to be a normal variant⁵, may not show heavy quinacrine fluorescence throughout the entire length of the long arm. Another possibility is that the distal portion of the long arm of the *Y* in this case (and possibly in other reported cases of unusually long *Y* chromosomes) represents a structural rearrangement. Morillo-Cucci and German⁶ have reported a *Y* chromosome which showed a terminal non-fluorescent segment which was interpreted as a *Yq*+, presum-

ably representing a duplication of a segment of the long arm of the *Y*. They do not state their reasons for deciding that the chromosome was partially duplicated rather than a normal variant. A description of the fluorescence patterns of variant and abnormal *Y* chromosomes is obviously needed.

The diagnosis of YY mosaicism in our patient is consistent with the exploratory laparotomy findings of mixed gonadal dysgenesis; namely, immature testicular tubular tissue in the left gonad and a right gonadal streak. The uterus, fallopian tubular structures and vagina were grossly normal for a prepubertal child. Three cell line-mosaicism was also found in gonad tissue culture, but of different proportions from those found in the skin (Table 1).

It is assumed that 45, X/46, XY/47, XYY is a result of non-disjunction following at least one division of a 46, XY zygote.

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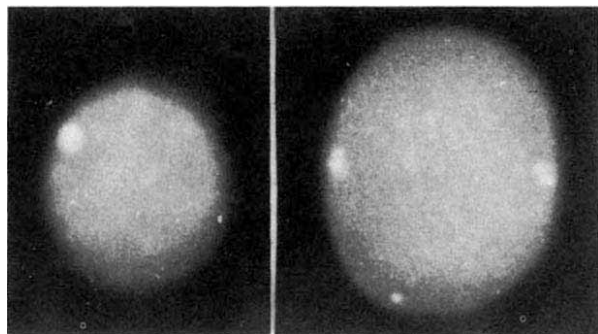


Fig. 2 Quinacrine fluorescence of interphase nuclei (fibroblast cells). Note one fluorescing *Y* body in nucleus on the left, and two fluorescing *Y* bodies in the nucleus on the right.



Fig. 3 Fluorescent photograph of quinacrine-labelled metaphase from fibroblast cell culture. The arrow indicates the *Y* chromosome. The bright fluorescence does not extend throughout the entire length of the long arms.

Impenetrability of the Mouse Placenta to Maternal Leukaemia Cells

THE concept of the placenta as a barrier separating the foetus from the immunological defence mechanisms of the mother¹⁻³ is in question. There is ample evidence that in humans foetal red cells are present in maternal blood during pregnancy⁴, and if red cells pass from foetus to mother, it is difficult to see why immunologically competent cells do not pass from mother to foetus. Tuffrey, Bishun and Barnes^{5,6}, using the *T6* chromosome marker, concluded that large numbers of maternal cells populate the organs of mice, while Billington *et al.*⁷, also using the *T6* marker, reached the opposite conclusion. Seller⁸, using a somewhat different experimental approach, also found no evidence for the passage of maternal cells into the foetus.

We have used a different system for testing the hypothesis that maternal cells cross the placenta into the foetus. Pregnant mice were inoculated with a virulent strain of leukaemia cells and, after appropriate periods of time, the foetuses were removed and injected into susceptible recipients. Death of the recipients from leukaemia would indicate that leukaemia cells

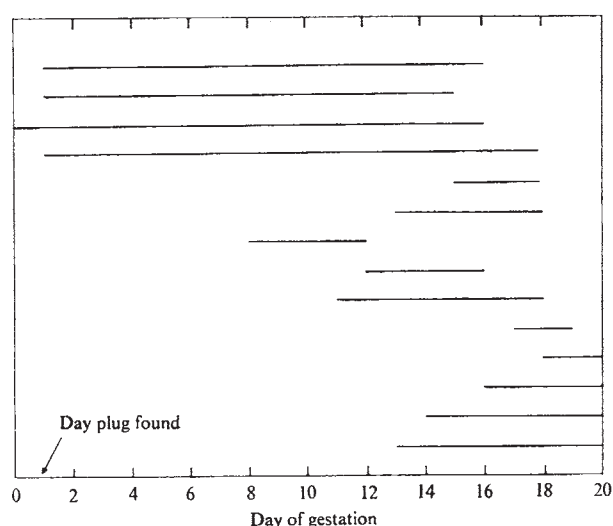


Fig. 1 Intervals between inoculation of pregnant females with tumour and preparation of foetal tissue for testing.

had crossed the placenta from mother to foetus. While transfer of leukaemia by this procedure might be attributed to viral agents, this was not a complicating factor in the interpretation of our experiments, for no evidence for the passage of leukaemia from mother to foetus was found in normal pregnancies.

L1210/MTX designates a virulent murine lymphocytic leukaemia which invariably kills its DBA/2 host. Survival time is related to the number of cells inoculated, but administration of very few cells can ultimately cause death⁹. In our experience, mice inoculated with 10^6 L1210/MTX cells die of leukaemia between 10 and 20 days later, and mice receiving 100 cells die between 15 and 30 days later. DBA/2 females which had been mated with DBA/2 males were injected intravenously with known numbers of L1210/MTX cells at various specific times during pregnancy or before mating. The pregnant females were killed at specific intervals after inoculation with the tumour, their uteri excised, and the foetuses removed (Fig. 1). Great care was taken to prevent contamination of foetuses with maternal blood or peritoneal fluid. In an attempt to kill any leukaemia cells carried on the surface of the foetuses by contamination from the mother, each foetus was dipped in 90% ethanol immediately after removal from the uterus, then rinsed carefully in Earle's balanced salt solution. Control experiments with embryos whose surface was deliberately contaminated with live tumour cells verified that the alcohol wash was capable of controlling surface contamination. The tissues of from one to four foetuses were then gently disrupted by a brief grinding in a glass and 'Teflon' tissue grinder. The tissue from each group of foetuses was then divided into three aliquots, each of which was injected into an adult female DBA/2 mouse. Development of leukaemia in the test mice would indicate the presence of tumour in the inoculum of foetal tissue which would indicate the passage of cells from mother to foetus. Test mice were always observed for 6 weeks for signs of leukaemia. Control experiments in which normal foetuses were injected with live tumour cells before being prepared as described above for injection into test mice established the ability of the assay procedure to detect embryos contaminated with as few as 100 tumour cells. Further control experiments used leukaemia cells labelled with 5-iodo-2'-deoxyuridine ($^{125}\text{IUDR}$) (ref. 10). Labelled cells were inoculated into foetuses, which were then prepared as described above and inoculated into test mice. The retention of ^{125}I was similar in such test mice to the retention in mice receiving living labelled leukaemia cells. ^{125}I is rapidly excreted when labelled non-viable tumour cells are inoculated into mice, so this test provides further evidence that the leukaemia cells were not damaged by preliminary passage through a foetus.

Table 1 Summary of Experiments which showed no Evidence of Leukaemic Cells in Foetuses Removed from Leukaemic Mothers

Days between inoculation of the mother and testing of foetal tissue	No. of pregnant mice inoculated	No. of leukaemia cells per pregnant mouse	No. of foetuses tested
2	8	10^7	29
3	6	10^7	24
4	8	10^7	27
5	5	10^7	23
6	5	10^6	16
7	5	10^6	16
8	2	10^5	5
14	2	10^3	8
15	4	10^3	20
16	1	10^3	12
17	1	10^3	3
Totals	47		183

Fig. 1 indicates the intervals between the inoculation of pregnant females with leukaemia cells and the removal of foetuses for testing. Because foetuses could not be excised with ease during early pregnancy, females inoculated very early in gestation generally received fewer leukaemic cells to permit their survival until late in pregnancy (Table 1). A total of 183 foetuses removed from forty-seven pregnant leukaemic mice were tested either singly or pooled with up to four litter mates. None of the 204 recipients of tissue from the 183 foetuses died from leukaemia, indicating that leukaemic cells were not transferred from mother to foetus.

Spleens and placentae from thirty of the leukaemic mothers were processed and assayed in the same manner as for foetal tissues. The recipients of these tissues invariably died from leukaemia, indicating that while leukaemic cells could not be detected in the foetuses, they were present in the spleens and placentae of the mothers.

To test the possibility that the foetus possesses some mechanism for inactivating or killing leukaemic cells, thirteen foetuses were inoculated with 10^4 or 10^5 leukaemic cells 1–3 days before they were removed from their mothers and prepared for assay in the usual manner. The subsequent death from leukaemia of all the test mice inoculated with these foetal tissues indicates that leukaemic cells do survive in foetuses, at least for the period studied.

Several investigators have noted that hyaluronidase can greatly increase the permeability of the placenta^{11–13}. In an attempt to determine whether or not hyaluronidase might alter placental permeability sufficiently to allow leukaemic cells to cross, seven mice on either day 9, 12, or 16 of pregnancy were inoculated with 10^6 leukaemia cells along with 1,000 units of hyaluronidase per day for 3 days. Twenty foetuses from these mice were assayed in the usual manner. Death from leukaemia occurred in recipients of three of the twenty foetuses. Each of the foetuses which caused the death of recipient mice was from a different mother. The absence of leukaemia in the litter mates of these foetuses indicates that the passage of leukaemia cells in hyaluronidase-treated mice is not a general phenomenon in the conditions of this experiment, but the occurrence of leukaemic cells in three foetuses suggests that further studies using hyaluronidase might provide a model system for investigating transplacental passage of maternal cells.

The experiments described here indicate that the pregnant mice from which the foetuses were removed were leukaemic, that leukaemic cells were invariably present in the placentae of those mice, that leukaemic cells can be recovered from foetuses by the methods used, and that leukaemic cells can survive in foetuses. In view of these findings, the fact that no leukaemic cells were detected in any of the 183 foetuses removed from otherwise untreated leukaemic mothers is an indication that white blood cells, at least those of this particular murine lymphocytic leukaemia studied, are not transferred from mother to foetus during gestation. These findings are

consistent with the observation¹⁴ that although pregnancy in humans with leukaemia has occurred very often, the occurrence of the disease in their babies, though reported^{14,15}, is rare.

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Homocysteine Metabolism in Scurvy, Growth and Arteriosclerosis

THE connexion between the oxidative and reductive properties of ascorbic acid and the metabolic and pathological abnormalities of the connective tissues in the disease known as scurvy has yet to be explained. Decreased synthesis of chondroitin sulphate has been found in scorbutic cartilage¹, and increased sulphation of proteoglycan fibrils results from increased synthesis of homocysteine in cultures of cells deficient in cystathionine synthetase². These observations, together with that of rapid non-enzymatic reduction of dehydroascorbic acid by homocysteine³, suggested that ascorbic acid catalyses the oxidation of homocysteine *in vivo*, and that homocysteic acid is a precursor of the esterified sulphate of connective tissue proteoglycans.

We have found that the conversion *in vivo* of ¹⁴C-homocysteine thiolactone to ¹⁴C derivatives differs in normal and scorbutic liver from guinea-pigs (Table 1); similar results were obtained with ³⁵S-homocysteine thiolactone. Homocysteine accumulated in scorbutic liver, but only traces were found in normal liver, from which most radioactivity was recovered as homocysteic acid, homocysteine sulphinic acid and other oxidized derivatives of homocysteine. The conversion to all these derivatives was diminished in scorbutic liver.

The conversion *in vitro* of ³⁵S-homocysteine thiolactone to ³⁵S-homocysteic acid, homocystine, and other oxidized deriva-

Table 1 Metabolism of Homocysteine in Guinea-pig Liver

Amino-acid	Normal	Scorbutic	Scorbutic microsomes	Scorbutic microsomes and ascorbic acid
Homocysteic acid	13.8%	<0.1%	<0.1%	1.72%
Homocysteine sulphinic acid	13.6	7.5	0.49	0.41
Homocystine	<0.1	49.8	29.1	15.5
Homocystine	<0.1	<0.1	3.1	9.7
Homocysteine thiolactone	trace	1.7	5.5	3.0
(Oxidized homocysteine derivatives)	68.8	38.7	5.7	9.4
Methionine	<0.1	<1.0	<1.0	<1.0
Adenosylhomocysteine	<1.0	<1.0	44.6	41.0
Cystathionine	3.3	2.3	5.2	12.2
Unidentified	—	—	3.7	4.4
Total % recovery	99.9	96.3	97.4	97.3

The conversion of ¹⁴C-homocysteine thiolactone to ¹⁴C-labelled amino-acids in extracts of normal and scorbutic liver is listed in the first two columns. 5.0 μ Ci carboxyl-¹⁴C-1-homocysteine thiolactone and 7.5 mg dl-homocysteine thiolactone in 10 ml. 5% dextrose were injected intraperitoneally, and after 1 h the livers were homogenized for 20–30 s in three volumes of cold sucrose-KHCO₃-KCl buffer¹¹. The extracts were deproteinized with sulphosalicylic acid, centrifuged at 10,000g for 10 min and chromatographed by the Stein-Moore method, counting aliquots of the fractions in Bray's solution. The conversion of ³⁵S-1-homocysteine thiolactone to ³⁵S derivatives *in vitro* is listed for scorbutic liver microsomes (column 3) and an aliquot of the same reaction mixture containing 2.3 mM ascorbic acid (column 4). The reaction mixture, containing liver microsomes 2.3 mg protein/ml., 0.1 M Tris, pH 7.4, and 0.5 μ Ci/ml. ³⁵S-1-homocysteine thiolactone, 5 μ Ci/ μ mol, was incubated at 37° C for 15 min, deproteinized with sulphosalicylic acid, centrifuged and chromatographed. The oxidized homocysteine derivatives, containing either ¹⁴C or ³⁵S, were eluted in a variable number of peaks between homocysteine sulphinic acid and homocystine; the compounds yielded ¹⁴C or ³⁵S homocysteic acid when chromatographed on paper, butanol-acetic acid-water.

tives, by scorbutic liver microsomes, was increased when a physiological concentration of ascorbic acid was present in a sample of the reaction mixture (Table 1).

The experiments recorded in Table 1 show that the rate of homocysteine oxidation was reduced in scorbutic liver, and that this was partially counteracted *in vitro* by a physiological concentration of ascorbic acid. This acid is converted to monodehydroascorbic acid by microsomal oxidation⁴, and, presumably, homocysteine is oxidized by monodehydroascorbic acid to homocysteic acid, through a series of derivatives corresponding to the various oxidation states of sulphur.

³⁵S-homocysteic acid was found to be a precursor *in vitro* of ³⁵S-labelled material which co-chromatographed with phosphoadenosine phosphosulphate, ³⁵PAPS (Table 2). Approximately equimolar quantities of ³⁵S and adenosine were found in the ³⁵PAPS peak. When the concentration of sulphate in the reaction mixture was increased the ratio of adenosine to ³⁵S was greater, indicating that there had been a reaction between inorganic sulphate and ATP to form unlabelled PAPS. The release of phosphate was dependent on homocysteic acid and ATP in the same reaction mixture, so that there was equimolar liberation of inorganic pyrophosphate from ATP (Table 2).

The formation of the esterified sulphate of proteoglycan from homocysteine was confirmed by culturing human skin cells to confluence in medium containing ³⁵S-homocysteine thiolactone, followed by dialysis of the homogenized monolayer against buffer containing EDTA and K₂SO₄, hydrolysis in 6N HCl, and amino-acid chromatography; 88% of the non-dialysable ³⁵S co-chromatographed with ³⁵SO₄, showing that homocysteine had been oxidized and esterified sulphate had been formed by the cultured cells.

In scurvy the slower oxidation of homocysteine to homocysteic acid (Table 1) would be expected to result in slower

Table 2 Reaction of Homocysteic Acid and ATP

³⁵ PAPS/ml./h	PPI/ml./h	³⁵ S/Adenosine	HCA/SO ₄
111 nmol	120 μmol	1.3	0.5
73		1.2	0.5
107		0.7	0.25

³⁵S-1-homocysteic acid, prepared by H₂O₂ oxidation of ³⁵S-1-homocysteine and purification by column chromatography, was incubated for 1 h at 37° C with guinea-pig liver microsomes. Each millilitre of the reaction mixture contained 2.5 μmol of 1-homocysteic acid, 5 or 10 μmol of K₂SO₄, 10 μmol ATP, 100 μmol Tris, pH 8.5, 10 μmol MgCl₂ and 1.5 mg microsomal protein. The mixture was heated at 100° C for 3 min, diluted ten-fold and chromatographed on BioRad AG1 chloride to separate ³⁵PAPS (ref. 12), and the ratio of ³⁵S to adenosine was calculated from the radioactivity and A₂₆₀ of the fractions in the peak. Homocysteic acid dependent phosphate release from ATP was determined by phosphate analysis of the 5% trichloroacetic acid supernatant fraction of an aliquot of the reaction mixture. The results are expressed as equivalents of inorganic pyrophosphate, since ADP failed to replace ATP in the reaction.

synthesis of PAPS from homocysteic acid (Table 2). PAPS is the precursor of sulphate esters⁵, and so decrease in any synthesis would be expected to diminish synthesis of sulphated proteoglycan components of connective tissues⁶, inhibiting growth, interfering with cartilage and bone formation, leading to the disintegration of blood vessels. Because of the intimate relationship between polymerized sulphated proteoglycans and tropocollagen polymerization⁷, defective wound healing and collagen formation in scurvy would also be expected to result from a reduction in the formation of PAPS and sulphated proteoglycan.

The demonstration of a pathway for the synthesis of PAPS from homocysteine in liver, the considerable inhibition of growth in scurvy, and the faster growth of normal young guinea-pigs injected with 80 mg/kg/day of homocysteic acid (my unpublished work) suggest that homocysteic acid has the properties of the sulphation factor which is believed to mediate the action of growth hormone⁸. The increased binding of ³⁵SO₄ by cultured cystathionine synthetase-deficient skin cells (ref. 2 and my unpublished work), which is probably a consequence of increased synthesis of homocysteic acid and PAPS from homocysteine, is comparable with the increased binding of ³⁵SO₄ by cultured cartilage fragments in the assay for sulphation factor.

Whereas a decreased rate of homocysteine oxidation leads to disintegration of blood vessel walls in scurvy, by decreasing the formation of sulphated proteoglycans, homocysteinaemia leads to accelerated arteriosclerosis, both in children with enzymatic disorders of sulphur amino-acid metabolism⁹ and in experimental animals¹⁰, by increasing the synthesis of sulphated proteoglycans in artery walls. I believe that the degeneration of elastic tissue, binding of lipoproteins, increased deposition of collagen, calcification and hyperplasia of myointimal cells observed in the vascular lesions associated with homocysteinaemia are secondary to increased production and excessive sulphation of arterial wall proteoglycans by myointimal cells, resulting from increased homocysteic acid and PAPS synthesis derived from homocysteine.

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Inhomogeneous Refractive Index in the Crystalline Cone of a Moth Eye

FROM investigations of arthropod compound eyes, Exner concluded that a dioptric effect in each ommatidium was due not only to the curved surfaces of the corneal facet and the cone tip, but also to a specific decrease of refractive index from the axis to the periphery of the dioptric apparatus^{1,2}. He called this refractive system a lens cylinder and assumed it to be present particularly in the dioptric systems of eyes which form superposition images. The first evidence of lens cylinder properties was presented for the cornea of the beetle *Hydrophilus*¹ and recent interference measurements have also demonstrated such properties in the pseudocone of the firefly eye³.

In contrast, Allen^{4,5} found no lens cylinder properties in the cones of the superposition eye of a moth, *Manduca sexta*. Using an interference microscope, he observed, in eyes embedded in maraglass, a homogeneous refractive index in the crystalline cone. He therefore concluded that the spherical surface of the corneal facet was the only dioptrically effective system acting like a collecting lens. In the eye of the moth *Ephesia kühniella*, however, erect images have been observed behind the crystalline cones which were produced by the cornea and crystalline cone⁶. Erect, real images cannot be formed by a single lens alone, and so the dioptric action of a collecting system must be inferred. This might result from an inhomogeneous refractive index of the crystalline cone, according to Exner. Consequently, we have tested the crystalline cones of the eye of *E. kühniella* for lens cylinder properties.

Fresh eyes of *E. kühniella* (mutant transparent⁷, without shielding pigment in the eye) were infused with gelatine. After solidification of the gel, they were sectioned with a vibrating razor blade⁸. The sections were viewed in transmitted light under an interference microscope (Zeiss Standard WL Pol-Interferenz). To ensure that the observed cone slices did not include the rounded cone tip, their geometry was checked with a differential interference contrast (Nomarski contrast) microscope.

Fig. 1a shows some slices of crystalline cones, sectioned normal to their optical axis. The three cones well in focus have a dark centre and alternating dark and light concentric rings, which are generated by interferential action. (They do not appear in a bright field microscope.) Each ring indicates a specific optical path length which is different for each ring in a given cone. Because the slices have constant thickness a concentric inhomogeneity of refractive index is apparent. This result is consistently observed. By compensation of the optical path length it was found that the refractive index was higher in the centre of the cone slices than in the periphery. (Quantitative measurements of refractive index in sections of known thickness are under way.)

Although these cone slices have no curved surfaces in the direction of incident light, a dioptric effect of each of them can be

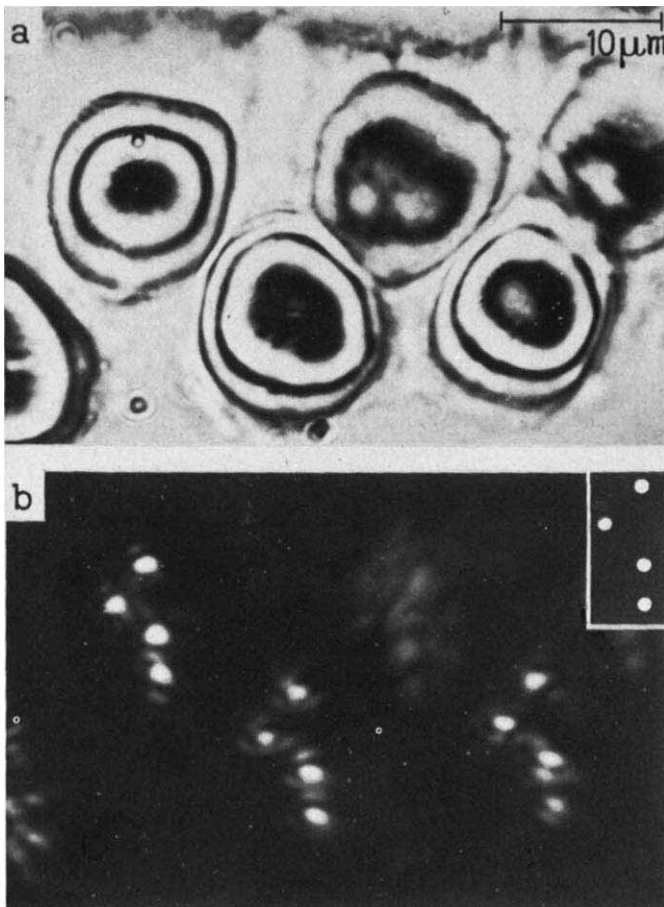


Fig. 1 *a*, Cross sections (10–15 μm thick) of crystalline cones as observed in the interference microscope. The interference rings in the cone slices are the expression of a radial variation of refractive index. *b*, Images of an object which is situated in front of the same preparation that was used in *a*. Each cone slice acts like a lenslet the focal lengths of three of which are about equal. Same scale as *a*. The inset shows the object, approximately actual size.

readily observed using the same preparation. The simplest procedure is to raise the microscope focus. A bright, small disk of light appears behind each cone slice. The image forming property of each cone slice can also be tested. In place of the microscope condenser, an object is installed which consists of four miniature lamps arranged in the form of the number 1. A real image of this object now appears behind each cone slice. In Fig. 1*b* this is shown for the three well focused slices of Fig. 1*a*, the images being sharpest about 25–30 μm above the preparation. (This distance varies with different preparations depending on the thickness of the section and its position in the cone.) The images are inverted relative to the object (allowance being made for the inverting action of the microscope). They appear as produced by collecting lenses. A collecting effect of a lens cylinder is possible only if the refractive index is highest at its axis. (An increase of refractive index from the axis to the periphery would result in a divergent lens. In this case only virtual images in front of the cone slices would be observed.)

The direct observation of refractive index in the sectioned crystalline cones, as well as the observation of their dioptric effect, provide proof of an inhomogeneous refractive index which decreases from the axis to the periphery of the cone. This result does not agree with Allen's findings of a homogeneous refractive index in the cones of the eye of *Manduca sexta*. We doubt whether interspecific differences can account for the disagreement. We rather believe that the procedures of fixation, dehydration and embedding in maraglass have obscured the result in the case of *Manduca sexta*. The observa-

tions presented here were done on essentially fresh material. Thus, Exner's conception of a lens cylinder originally derived from the beetle superposition eye may be extended to the eucone superposition eye of the moth.

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Metabolic Rate independent of Temperature in Mollusc Tissue

THERE is considerable controversy about the possible occurrence of temperature-insensitive regions in poikilotherm rate-temperature (R-T) curves. Newell and Northcroft^{1,2} reported that the metabolism of a number of marine intertidal invertebrates is essentially independent of temperature, and not influenced much by short term temperature fluctuations within the normal environmental range. This temperature-insensitive region is visible as a plateau in the R-T curve. Newell and Northcroft also presented evidence to suggest that the precise position and extent of the temperature-insensitive region on the R-T curve vary, in accord with long term variations of the environmental temperature. They suggested further that such metabolic stability is of considerable adaptive significance in intertidal animals, which live in a rapidly fluctuating thermal environment. Davies and Tribe³ disputed the existence of temperature-independent metabolism. They found no evidence of Q_{10} values approaching unity (except at high temperatures) in the respiration rates of intact crabs or limpets. Similarly, they could detect no regions of temperature-independence in excised limpet mantle or crab gill. They suggested that previous reports of temperature-independence may be attributable to experimental techniques. Recently, while investigating seasonal shifts of metabolism in excised tissues of the American oyster, *Crassostrea virginica* Gmelin, we obtained results that support the concept of temperature-independent metabolism as a tissue level homeostatic mechanism.

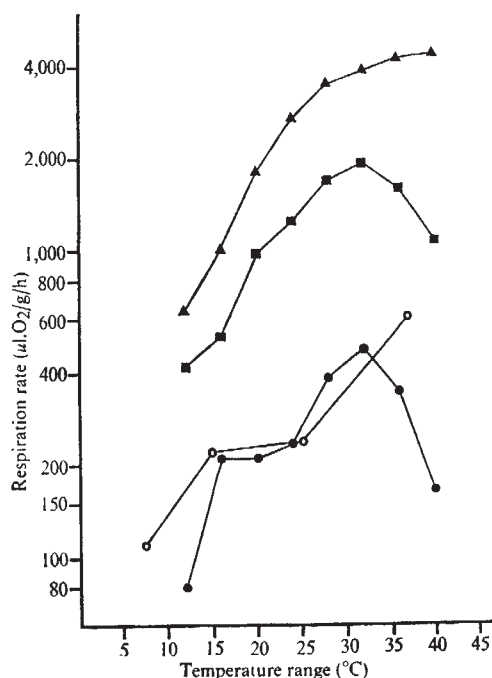
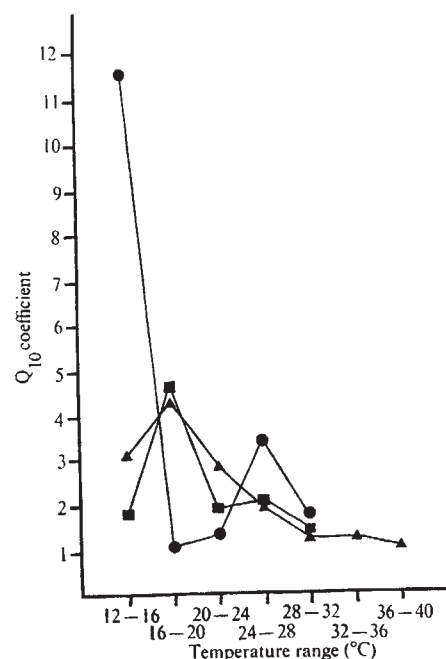
Three tissues were used; gill, mantle and adductor muscle. Gills were excised and several squares (with dimensions of approximately 5 mm) were cut from each of the demibranchs. In the preparation of mantle tissue the lobulated border was discarded and the remaining central free portion was cut into three or four pieces. The adductor muscle consists of a translucent firm portion and a fibrous white portion, but we used only the vitreous translucent portion. Small blocks of the muscle tissue were thinly sliced with a device designed by Deutsch and described by Cohen⁴. Respiration rates were determined by the Warburg technique, using flasks of approximately 15 ml. capacity. The medium consisted of 1.5 ml. of filtered sea water, adjusted to a specific gravity of 1.025. The shaking rate was 120 strokes per minute; air was the gas phase. Respiration rates (in $\mu\text{l. O}_2$ per g dry weight per h) were determined at 4 degree intervals from 12° to 40° C, but the respiration rate of each sample was measured at one temperature only.

Table 1 Influence of Temperature on Respiration Rates of Excised Gill, Mantle and Adductor Muscle of *C. virginica*

Temperature (°C)	Gill QO ₂ ± s.e.	Mantle QO ₂ ± s.e.	Adductor QO ₂ ± s.e.
12	639 ± 54	421 ± 30	80 ± 11
16	1,008 ± 38	531 ± 57	213 ± 8
20	1,815 ± 67	982 ± 29	212 ± 16
24	2,761 ± 98	1,266 ± 113	238 ± 25
28	3,564 ± 111	1,695 ± 132	388 ± 54
32	3,881 ± 246	1,951 ± 103	485 ± 72
36	4,307 ± 462	1,613 ± 115	350 ± 24
40	4,418 ± 522	1,081 ± 179	165 ± 9

It is clear from Fig. 1 that although gill and mantle respiration rates do not have an "intermediate plateau", muscle respiration has a distinct temperature-independent region extending from 16° to 24° C. The R-T curve for *Mytilus edulis* foot retractor muscle respiration plotted from the data of Glaister and Kerly⁵ has a similar region of temperature independence. The correspondence between the R-T curves for the two muscle tissues is all the more impressive in view of the considerable differences in preparative technique; the adductor muscle was sliced thinly and suspended in natural sea water with air as a gas phase, while the foot retractor muscle was used intact and suspended in buffered artificial sea water with oxygen as a gas phase. Also, the distinct differences in the Q₁₀ curves (Fig. 2) of the different oyster tissues that were determined in similar experimental conditions indicate that the "intermediate plateau" is not dependent on technique, but is an endogenous characteristic of adductor respiration. The biochemical basis for the response is still unclear. Further comparative study will be required to establish whether or not such regions of temperature-independent metabolism are characteristic of molluscan muscle tissue in general. The data presented here, and the demonstration of temperature insensitive regions in the heart rates of two species of oysters by Takatsuki⁶, suggest that they are.

The apparent absence of "intermediate plateaux" in the R-T curves for respiration of intact oysters⁷ is understandable when the low metabolic rate of muscle relative to that of gill and mantle tissues is considered.

**Fig. 1** Rate-temperature curves for respiration of excised gill (▲), mantle (■) and adductor muscle (●) of *C. virginica*. Data for *Mytilus edulis* foot retractor muscle (○) from Glaister and Kerly⁵.**Fig. 2** Q₁₀ coefficients for respiration of excised gill, mantle and adductor muscle of *C. virginica* (symbols as in Fig. 1).

The adaptive significance of the temperature-independent respiration of the muscle tissue may be related to the fact that the adductor muscle is one of the principal defensive mechanisms of the bivalves and, as such, should ideally be relatively independent of environmental fluctuations. This interpretation is supported by the results of Percy, Aldrich and Marcus⁸ who found that although the respiration of oyster gill and mantle tissues exhibited inverse seasonal thermal acclimatization, adductor muscle respiration showed partial seasonal acclimatization.

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Right Hemisphere Specialization for Depth Perception reflected in Visual Field Differences

THE two cerebral hemispheres in man function differently; the left hemisphere has a special function in processing language material while the right hemisphere has a special function in the perception of visuospatial material^{1,2}. It has been suggested³ that these functional differences are reflected in perceptual asymmetries favouring the visual field opposite the predominant hemisphere. As a consequence of left hemisphere specialization in processing language material, words or letters presented successively to either visual field are more readily

recognized in the right visual field. Conversely, visuospatial location, a predominantly right hemisphere function, is more accurate in the left visual field⁴.

We have examined the role of the right hemisphere in depth perception, another aspect of visuospatial ability that might be expected to show lateral perceptual asymmetries. All experiments followed the procedure of successive random tachistoscopic presentations to the left or right visual fields. The subject fixated a central point in the pre-exposure field and after a "ready" signal the stimulus was presented briefly to the left or right of the fixation point. Practice sessions preceded all experimental sessions to familiarize the subject with the procedure and to assure the experimenter that the instructions were understood.

For the first experiment we used a model T-2B-1 Gerbrands Harvard tachistoscope (a mirror tachistoscope) with a back attachment for three dimensional viewing. Two illuminated vertical rods were viewed for 90 ms through a one inch slit which extended the width of the exposure field. The central rod was stationary and the other was mounted on one of two sliding tracks positioned to the left and right of centre. The adjustable rod was set, in a prearranged random order, 7, 14, 21 or 28 mm in front of or behind the central rod and approximately 4 degrees to the left or right. The subject was asked to judge whether the central rod was closer or farther than the other. The maximum number of correct responses per field was thirty-two.

The mean number of correct judgments in the left visual field was significantly greater than in the right visual field ($F=4.93$, d.f.=1,20, $P<0.05$) (Table 1).

Table 1 Mean Depth Discrimination Scores for Left and Right Visual Fields under Three Conditions

Stimulus	Viewing condition	Exposure time (ms)	N	Field		F ratio
				Left	Right	
Vertical rods	Binocular	90	22	20.36	18.59	4.93 *
Vertical rods	Monocular	100	20	19.40	19.05	0.13
Random dot stereograms	Stereoscopic	120	20	10.05	7.80	7.25 *

* $P<0.05$.

The same task was then presented to a new group of subjects using a monocular viewing condition, to see whether monocular cues alone would result in visual field differences. To equate the difficulty level of the binocular and monocular tasks, the exposure was extended to 100 ms and larger distances were introduced between the central and adjustable rods (1, 2, 3 and 4 inches). There were no visual field differences in monocular viewing conditions (Table 1). It seemed therefore that binocular input was necessary to demonstrate left field superiority on this form of depth perception task.

The next experiment was designed to examine binocular disparity, by which the left eye's view of an object in space differs from the right eye's view of the same object. Random dot stereograms⁵ were used as stimuli for this task. We realized, after beginning our study, that Carmon and Bechtholdt⁶ had demonstrated that stereoscopic perception of such patterns is affected by lesions of the right hemisphere, which is, of course, in agreement with our findings. Because the model T-3B-1 Gerbrands Harvard tachistoscope does not have separate channels for each eye it was adapted to stereoscopic viewing by placing polaroid linear filters appropriately over the eyepieces and viewing channels. Ten different stereoscopic pairs were constructed, and each, when viewed stereoscopically, gave the experience of two depth planes with a central form appearing in front of the background. The left and right eye patterns were identical except that a central portion of the right eye's pattern was shifted approximately 17 minutes of

arc horizontally to the left compared with the position of that identical portion in the left eye's pattern. Fusion of the disparate left and right eye images was necessary for identification of the central form. Each pair was viewed stereoscopically for 120 ms in either the left or right visual field. The distance from fixation point to the closest edge of the stimulus form subtended a visual angle of approximately 2 degrees. The subject merely named the central figure (triangle, circle, rectangle and so forth). The mean recognition score for the left and right visual fields are presented in Table 1. Left field scores were significantly higher than right field scores ($F=7.25$, d.f.=1,18, $P<0.05$).

The only cue to depth perception present in the latter task was binocular disparity. At brief exposures therefore fusion of left and right eye images at a central level was more efficient when the stimuli were presented to the left visual field. This finding and the findings on the three dimensional depth task suggest that the right hemisphere is more efficient than the left in dealing with binocular input. These studies and others on visual point localization⁴ suggest that the functional specialization of the right hemisphere for complex visuospatial functions may be based on its predominance for fundamental visual processes.

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Effects of Actinomycin D on Memory and Brain RNA Synthesis in an Appetitive Learning Task

CURRENT selectional models of learning and memory¹⁻³ suggest that messenger RNA (mRNA) is implicated in biochemical processes in the brain which mediate long term memory. The role assigned to mRNA in these models is that of a carrier of information to the ribosome complex from environmentally stimulated derepressed regions of the DNA molecule. The specific protein molecule or peptide thus produced is supposed to signpost or colour-code neurones in such a way that conduction of subsequent impulses, similar to that which first specified the existence of the molecule, is facilitated. The loss of RNA from such a system should prevent the production of the specific protein molecule and impair the formation of a permanent memory trace, but experiments which have attempted to prevent the synthesis of mRNA by means of actinomycin during avoidance learning have given ambiguous results⁴⁻⁷. We have therefore set out to determine, in an appetitive learning situation, the time after acquisition at which actinomycin becomes effective in impairing memory, the extent of diffusion of the drug vehicle through brain tissue and the effect of the quantities of the drug used on brain RNA synthesis.

In the first experiment, twelve three month old male hooded Lister rats (250-300 g) were used as subjects. A cannula was stereotactically implanted in each hippocampal area (A, 3.0, L, 3.0, see ref. 8) to a depth of 2.5 mm. Seven days after surgery,

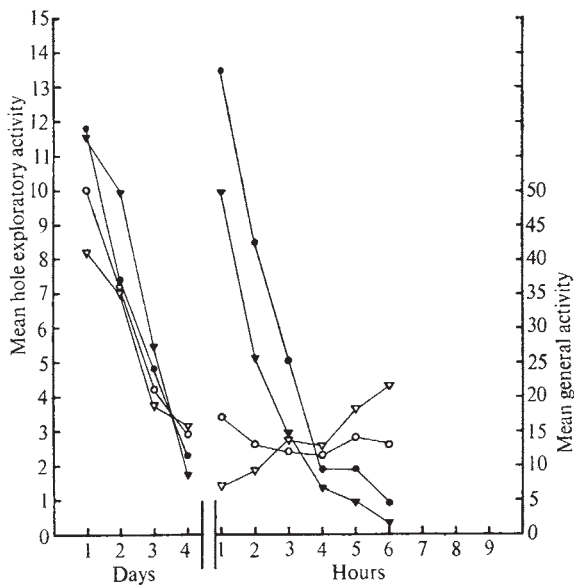


Fig. 1 Mean HE and GA scores before and after injecting actinomycin in 0.9% NaCl. Hourly recall tests were made after the acquisition trial on day 5. Day 4 weighted HE and GA scores in the two groups were not significantly different. Actinomycin had no apparent effect on memory or recall of memory. ●, HE saline; ▼, HE actinomycin; ○, GA saline; ▽, GA actinomycin.

the rats were placed on a 23.5 h water deprivation schedule. The apparatus⁹ consisted of a white aluminium box with a smaller black box attached to one side. The smaller box was large enough to accommodate a rat's head and implanted cannulae. A water valve was fixed in the middle of the rear wall of the smaller box, but water was available from it only for 10 s on day 5 of the experiment. A photo-electric cell assembly mounted just inside the opening to the smaller box made it possible to count the number of times a rat's head entered the smaller box during a test period, called the hole exploratory activity (HE). The floor of the larger box was a stabilimeter which measured the general motor activity (GA) of each subject.

On day 1 of the experiment, each rat was placed in the apparatus; the lid was secured and HE and GA were recorded over a 4 min period. Water was not available in the apparatus. This procedure was repeated on days 2, 3 and 4 to habituate the rats to the apparatus and establish baseline levels of HE and GA. On the basis of HE scores on day 4, the rats were divided into two equal groups, those with similar scores being grouped together. Four hours before being placed in the apparatus on day 5, the rats in the experimental group received an injection in the hippocampal area of 10 µg of actinomycin dissolved in 10 µl of 0.9% NaCl. The injections were made at a depth of 3 mm through the implanted cannulae. Rats in the control group received equal volumes of 0.9% NaCl. The water valve was connected to a water supply and each subject was allowed to drink for 10 s before being removed to its home cage. This was the acquisition trial, when HE and GA were not recorded. After the acquisition trial the rats were not allowed the normal 30 min access to water in the home cage. Six successive 4 min recall tests were made at hourly intervals starting one hour after acquisition. Water was not available during the recall tests and HE and GA were recorded.

The mean HE and GA scores for each group are given in Fig. 1. The scores of each rat on day 4 were subtracted from those recorded during hours 1 to 6 and the weighted data were analysed statistically using the *F* test for homogeneity of variance and the *t* test¹⁰. No significant differences were detected in either HE or GA scores between the two groups at the *P*=0.01 level of significance. This indicates that learning

and memory for this task, over the period investigated, were not affected by actinomycin. But because memory over the first 3 h after acquisition occurs independently of a 95% inhibition of protein synthesis^{11,12}, memory over the first 3 h in this experimental situation was unlikely to be affected by an inhibition of mRNA; differences were only expected at times after the first 3 h. A possible reason for the apparent similarity in HE scores in the two groups (Fig. 1) is that there was a rapid re-habitation or extinction in the control group during hours 1 to 6. The very sharp reduction in HE activity during hours 2 to 4 in the control group contrasted with results from previously tested saline-injected control rats in this situation¹³. The reduction in response in the control group may have obscured a possible memory deficit in the experimental group at hours 4, 5 and 6 after acquisition.

If the rapid extinction or re-habitation in the control group had obscured a memory deficit in the experimental group, then allowing 4 h to elapse before testing the subjects for recall would evaluate the possibility of both extinction and re-habitation and the hypothesis that memory, following an injection of actinomycin, is impaired only at 3 h or later after acquisition.

Twelve rats were prepared as described and habituated to the apparatus during days 1 to 4. Injections were given 4 h before the acquisition trial on day 5. After acquisition, the rats in six experimental and six control groups were left in their cages, without water, for 4 h before being replaced in the apparatus for the first recall test. Subsequently, recall tests were made at hourly intervals from hours 4 to 7.

The mean scores for HE and GA for each group throughout the experiment are given in Fig. 2. The statistical analysis of the day 4 weighted data from hours 4 to 7 showed that the HE scores of the experimental group were significantly smaller (*P*=0.01) than the control group. The GA scores of the two groups were not significantly different. Fig. 2 shows clearly that the subjects which had received actinomycin behaved as if they had not experienced water reinforcement.

Because of the physical restraints of the drug's solubility in 0.9% NaCl and the probability of causing significant lesions with injections of more than 10 µl, injections were limited to 10 µg actinomycin in 10 µl of 0.9% NaCl. The extent of diffusion of the drug through brain tissue over 4 h was estimated

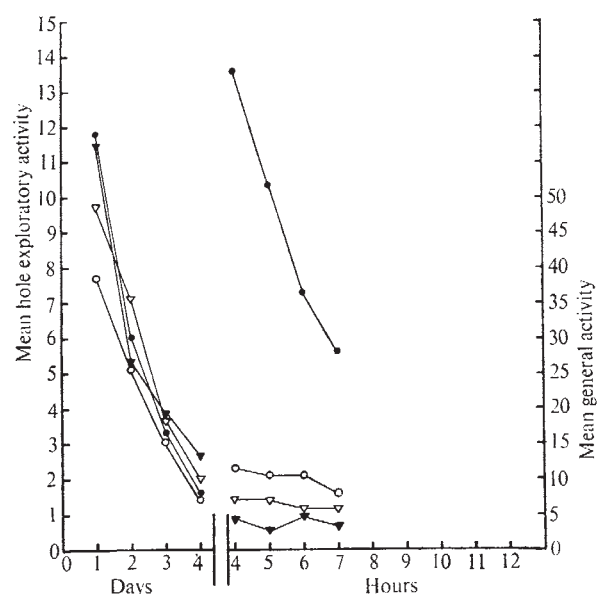


Fig. 2 Mean HE and GA throughout the second experiment. Actinomycin in 0.9% NaCl was injected 4 h before acquisition. Hourly recall tests started at hour 4 after acquisition. Day 4 weighted scores were not significantly different, but similarly treated HE scores differed significantly (*P*=0.01) at hour 4 and at later times. Symbols are as in Fig. 1.

in eight rats by injecting 10 μ l. of a 2% solution of Evans blue dissolved in 0.9% NaCl. Four hours after injection, the rats were killed and their brains were dissected out, frozen in CO₂ syrup¹⁴ and sectioned at 40 μ m intervals on a freezing microtome. The area of diffusion was in the shape of an ellipse around the point of injection, and was 7.6 mm long, 3.2 mm high and 3.4 mm wide. The dye penetrated anteriorly to the septal area and posteriorly to the neocortex above the superior colliculi. The spread in the vertical plane, at the point of injection, extended from the ventral thalamus to the top of the hippocampus. Laterally, the dye diffused across the hippocampus as far as the border of the lateral ventricle. On the basis of these findings, the percentage of RNA inhibition was determined in the hippocampus, thalamus and medial neocortex after hippocampal injections of either 10 μ g of actinomycin in 10 μ l. of 0.9% NaCl or 10 μ l. of 0.9% NaCl. Six subjects received actinomycin and six received the vehicle. 4 μ Ci of 6-¹⁴C-crotic acid was injected into the brains of these rats, 4 h after the initial injections, at a depth of 3.0 mm in both hemispheres at the coordinates A, 2.0, L, 3.0⁸. All rats were killed 4 h later and the RNA was extracted from hippocampal, thalamic and medial neocortical tissue by the method of Scherrer and Darnell¹⁵. The specific activity of the RNA was measured in Bray's solution in a liquid scintillation counter; optical density was read at 260 nm. The results are given in Table 1; they show that the greatest inhibition of RNA synthesis was in the hippocampus, with RNA synthesis in the medial neocortex being the least inhibited.

Table 1 Incorporation of 6-¹⁴C-Crotic Acid into Brain RNA

	0.9% NaCl specific activity mean c.p.m./A ₂₆₀	Actinomycin specific activity mean c.p.m./A ₂₆₀	Inhibition (%)
Hippocampus	553	255	54
Thalamus	530	345	35
Medial neocortex	518	456	12

The results of these experiments indicate that actinomycin does not affect acquisition of memory, or memory immediately following acquisition, but that it does impair memory 4 h after acquisition and at later times.

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Failure of Visual Estimation of Motion under Strobe

WEINBERGER¹ poses an interesting conjecture that the retinal image size of an object and its rate of change are the primary data used by the visual system to estimate the "time interval to juncture" (that is, when it will hit you). As one clue that the concept may be correct, I should like to offer the following observation which seems to indicate that at least some retinal measurement of rate is necessary in impact estimation.

Lately there has been a fad in this area for dances to be held under stroboscopic lighting. The powerful, intermittent flashes produce an illusion of unreality. This mental impression is partially attributable (I think) to the viewer's inability to predict the future position of other dancers from the visual appearance of a series of stationary images; each strobe flash creates an entire still picture of the dance scene in the mind of the viewer, with no retinal clues regarding motion except those calculated in the mind from a succession of still images. I can attest to the fact that mental calculations of this sort are very poor and slow, compared with the ordinary perception of velocity obtained in sustained light. In stroboscopic lighting we have tried to toss a beanbag back and forth at short range. This is normally a simple task, but under a strobe it is very difficult to make a successful catch even though the flash rate provides 5 or 10 images along the trajectory. One feels foolish but helpless observing the short flight as the beanbag arcs gracefully (in steps) over to strike the body in the vicinity of the hands. Clearly, position information alone is inadequate for motion estimation. One's ability to throw is unimpaired, as might be expected since it is based on target position.

In connexion with Weinberger's suggestion, I recall that I was aware of the beanbag's true size and distance, but apparently the trajectory was calculated too slowly to be of use in catching the bag.

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Excavation of Two Mesolithic Shell Middens on the Island of Oronsay (Inner Hebrides)

BETWEEN 1881 and 1913 three Mesolithic "shell midden" sites were excavated on the Island of Oronsay in the Inner Hebrides¹⁻⁵. These sites are important because they preserve excellent evidence for the economic and subsistence activities of human groups in the late pre-agricultural phase of British prehistory; in fact, comparable information on these aspects of life is currently available from only two or three other sites in Britain.

Unfortunately, the data obtained during the early investigations on Oronsay are now considered unsatisfactory for several reasons. The most conspicuous gaps in the evidence relate to: (1) the relative and absolute ages of the different middens; (2) the range and relative importance of the different food supplies exploited; (3) the size and composition of the social groups responsible for the middens; (4) the lengths of time and seasons of the year during which the sites were occupied; and (5) the nature of environmental conditions which prevailed during the Mesolithic occupations.

We aimed to correct the deficiencies in the existing data by excavating some samples of midden material from carefully controlled stratigraphic horizons. We water sieve the excava-

ted material through mesh sizes of respectively 2 mm and 1 mm; the residues retained by the sieves are being sorted at present by eye, but we hope eventually to devise mechanical means to facilitate this procedure. The data obtained from the excavations will be amplified in two principal ways: (1) by a series of borings to determine the total area covered by each midden; and (2) by a detailed series of investigations—pollen analyses, $^{18}\text{O}/^{16}\text{O}$ studies of sea temperature, studies of sea-level changes and coast-line development and the like—designed to throw light on the natural conditions in which the Mesolithic groups lived.

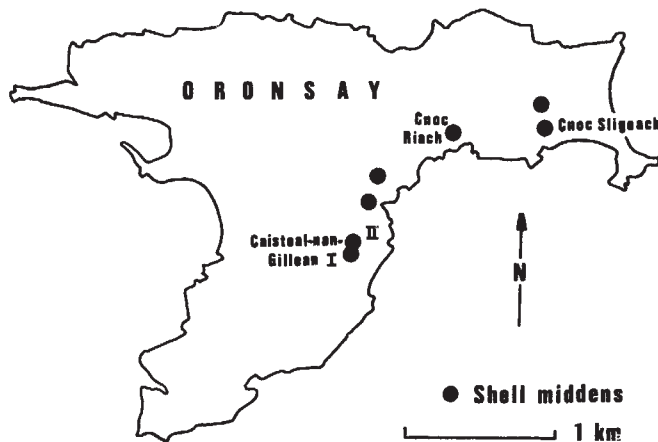


Fig. 1 Map of shell middens on Oronsay. The three named sites (Cnoc Sligeach, Cnoc Riach and Caisteal-nan-Gilleann I) have been known since the nineteenth century. The remaining sites have not previously been recorded in the literature.

Small scale exploratory excavations were carried out on two of the Oronsay middens during August 1970. Excavations at Cnoc Sligeach revealed two distinct layers of midden deposit separated by up to 1 m of wind-blown sand. The lower deposit was by far the richer and consisted of a 55 cm thick accumulation of shells and other occupation debris interspersed within a dark brown sandy matrix. The upper deposit had an average thickness of only 5–10 cm, but this too produced a rich accumulation of cultural material. At the second site (a previously unrecorded midden located immediately to the north of the well known site of Caisteal-nan-Gilleann) excavations revealed a single midden deposit with an average thickness of 40 cm; the only hint of discontinuity in the formation of this deposit was provided by a very thin (2–3 cm) layer of sterile sand 10–15 cm from the surface of the midden.

Although the excavated material is still being analysed, several interesting facts have emerged. The most important observation from an economic viewpoint is the great abundance of fish bones in the shell material. Indeed, preliminary estimates suggest that sea fish may have contributed as much to the diet of the midden occupants as did the shell fish of which the mounds at first sight appear to be totally composed. Small samples of fish bones have been examined by Dr A. C. Wheeler of the British Museum (Natural History) who reports that most belong to the saithe (*Pollachius virens*), a fish which is still abundant in the coastal waters around Oronsay. (No reference whatever to this species of fish appears in the report on the earlier investigations at Cnoc Sligeach—presumably because the bones are too small to have been detected with the methods of excavation used³. This observation alone provides an ample demonstration of the need for very fine sieving of deposits when excavating sites of this nature.) Other species of fish identified so far include the ballan wrasse (*Labrus bergylta*), thornback ray (*Raja clavata*), small spotted dogfish (*Scylliorhinus caniculus*), ling (*Molva* sp.) and what seems to be a freshwater salmonid (*Salmo* sp.).

The remainder of the food refuse from the middens is awaiting expert identification. Most of the sea shells from both the sites excavated belong to the common limpet (*Patella vulgata*); there are smaller numbers including the common periwinkle (*Littorina littorea*), dog whelk (*Nucella lapillus*), oyster (*Ostrea edulis*), cockle (*Cardium edule*), scallop (*Pecten maximus*) and razor shells (*Ensis* sp.). Remains of crabs and lobsters also occur abundantly throughout the middens; bones of birds and mammals, on the other hand, are comparatively scarce and for the most part they are fragmentary.

Definite artefacts recovered so far include several characteristic "limpet scoops" (made from both stone and deer antler), and several flattened pebbles which evidently served as either hammer or anvil stones. Flint flakes are fairly common, but the only definite tool forms which can be identified are several heavily worked (or utilized) *lames ecaillés*; our hope that fine sieving of deposits would produce distinctive "microlithic" forms has not as yet been realized.

A careful search for further shell middens on Oronsay revealed at least four new sites in addition to the three (Cnoc Sligeach, Cnoc Riach and Caisteal-nan-Gilleann I) already recorded in the literature (Fig. 1)⁵. All these sites lie along the less exposed south-eastern coast of the island and none is more than 400 m from the present shore. Levelling measurements carried out by Mr J. E. Gray, of the University of Aberdeen, revealed further that all of the middens lie at approximately uniform heights of between 10 and 15 m above present day mean sea level. This height corresponds well with that of the main postglacial shoreline in western Scotland and is consistent with the view that the sites were occupied during the well documented sea-level stand at this elevation⁶. The relationships between the shell middens and the clear traces of raised beach deposits preserved at several points on Oronsay are at present being studied by Dr W. G. Jardine of Glasgow University.

We hope that our investigations on Oronsay will continue for at least two further seasons. The chief objectives of future work will be: (1) to excavate further portions of the two sites already sampled in order to assess the extent of lateral variability in the contents of the middens; and (2) to extend the present investigations to several other middens on Oronsay. Clearly, one of the most interesting aspects will be to compare the different sites with respect to a number of different features—age, exploitation of varying food resources, season of occupation and so on. A further objective which may or may not prove feasible with the resources available will be to excavate larger areas of one or more of the middens in the hope of locating some traces of dwelling structures.

The 1970 investigations were supported by a generous grant from the Association for Cultural Exchange. We thank the owner of Oronsay, Lord Strathcona, for permission to excavate the sites, and the farmer, Mr Andrew Macneill, for his cooperation.

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⁴ Grieve, S., *The Book of Colonsay and Oronsay* (Oliver and Boyd, Edinburgh, 1923).

⁵ Lacaille, A. D., *The Stone Age in Scotland* (Oxford University Press, 1954).

⁶ Sissons, J. B., in *The Geology of Scotland* (edit. by Craig, G. Y.), 467 (Oliver and Boyd, Edinburgh, 1965).

BOOK REVIEWS

Nagel's Message

Philosophy, Science and Method: Essays in Honor of Ernest Nagel. Edited by Sidney Morgenbesser, Patrick Suppes and Morton White. Pp. ix + 613. (Macmillan: London, January 1971.) £5.50.

Festschriften are for men who have put their stamp on some branch of enquiry during a certain period of time. By this token, the present volume is well deserved, for Ernest Nagel's writings have become the classical expression of current views on the philosophy of science as developed between 1930 and 1960, spanning as they do two major texts from Nagel's hand on that subject, his *An Introduction to Logic and Scientific Method* (in conjunction with Morris Cohen, 1934) and his magisterial *The Structure of Science* (1961). Equally well known is Nagel's *Principles of the Theory of Probability* which, appearing in the late thirties, is still one of the classics on the subject. Nagel took what is best from the tradition of logical empiricism and combined it with his deep knowledge and understanding of the principles of the natural and social sciences to yield authoritative instruction which, being written in a superbly lucid style, has served as an inspiration to all practitioners in the subject.

The new volume is an apt expression of the debt which the present generation of philosophers owes to Nagel. Its thirty essays cover a widely ranging field, from formal studies on induction, confirmation theory and epistemological foundations; critical articles on the logical problems raised by the various sciences such as biology, linguistics, social anthropology, to a section on foundations of economics and moral theory. Particularly, there are no contributions commemorating one of Nagel's major preoccupations, the philosophy of history, but to make up for this, there is a section including a number of weighty historical studies, such as Marshall Clagett's "The Quadrature by Lunes in the Later Middle Ages" (probably an anticipatory echo of Nagel's little volume—in conjunction with J. R. Newman—on Gödel's Proof), I. Bernard Cohen's demonstration of Newton's continuing interest in theological issues throughout his life and a perceptive study by A. Koslow on the law of inertia, which seeks to dispel a

number of apparently erroneous views which have been held about the logical status of this law.

Within the confines of a short review it is quite impossible to do justice to the different contributors. Certainly this volume is valuable because it indicates clearly what is meant by "philosophizing" about science while putting before us, through a microscope as it were, contemporary specimens. It would thus be invidious to single out individual contributions, except where, in my opinion, they manifest something of special interest by throwing light on developments that are taking place at present on the philosophical stage, issuing often from some of the tenets of Nagel's own philosophy.

Mary Hesse with her usual expertness seeks to salvage something from Nagel's objections to quantified confirmation theory, discussing in particular Carnap's notion of "instance confirmation"—confirmation over finite domains. Sidney Morgenbesser once again attempts to clarify issues surrounding realism and instrumentalism, so expertly defined in Nagel's own *Structure of Science*. In a similar vein and of especial interest is Carl Hempel's discussion of the issues that arise marginally in connexion with the problem of reduction, because here Hempel attempts to settle accounts with certain developments in philosophy of science, due above all to Paul Feyerabend, which for a while at least appeared to put paid to the whole basic approach of which Nagel and Hempel are the prime expositors; in particular, the doctrines of deductivism and of meaning that are part of the assumptions of that viewpoint. In a similar vein, Max Black's brief but amusing "Some Half-Baked Thoughts about Induction" is a valiant attempt to rescue inductivism from recent criticism of this notion.

Meaning is also a topic discussed in an important contribution by Noam Chomsky, attacking the basic assumptions lying behind the empiricist theory of the acquisition of knowledge, with a sustained critique of the views of Quine and Wittgenstein.

Finally, one must pay tribute to an elegantly executed demonstration of the weaknesses of the "identity-theory" of the mind-body relationship by Judith Jarvis Thomson.

This list by no means exhausts the riches to be found here, and if the different chapters are short and succinct, this is a special gain for those readers of this journal who, while not professionals, perhaps would like to see in the rarefied regions that lie at the borderlines of their science something of the real scholarship that lies at the logical foundations of their everyday pursuits. GERD BUCHDAHL

Is Awareness Real?

Facing Reality: Philosophical Adventures of a Brain Scientist. By John C. Eccles. (Heidelberg Science Library, Vol. 13.) Pp. xi + 210. (Springer-Verlag: New York and Berlin, 1970.) \$6.20.

THIS collection of essays and accounts of neurophysiological research ranges from detailed considerations of coding of information and synaptic properties to the general nature of human experience and morality. Sir John Eccles is well known for his original contributions over this broad field and this collection of his writings is to be welcomed as representing the work and thoughts of a biologist who has produced first rate scientific contributions and is also concerned with man's place in the universe.

The book starts with a clear and concise account of the "neuronal machinery of the brain" and goes on to considerations of how selfconsciousness came to man and possibly to other possessors of brains. There is a particularly interesting essay, "The Understanding of Nature", written (though later withdrawn) for a volume on the philosophy of Karl Popper and concerned with the concept of science as "a woven web of guesses". Eccles praises Popper for allowing scientists to look on their blind alleys and mistakes as progress and achievement. Eccles does (though understandably) try to have it both ways here; by expressing gratitude to Popper for allowing him to accept his original theory of synaptic transmission as useful though wrong, and to be pleased with its later partial acceptance. In these writings, as elsewhere, he is not afraid to touch on theology. The reader may experience unease: do considerations of neural activity take us closer than social behaviour to moral and theological

issues? Possibly, but a clear case is not made out.

Eccles takes consciousness, awareness, seriously. This he sees as a great mystery, to be explained and described in terms of neural activity. On this most difficult subject Eccles raises questions bravely, but hardly in a form amenable to experimental treatment or to philosophical analysis. One would have liked the alternative philosophical positions stated and related to existing neurological data or, failing this, to foreseeable experiments with postulated outcomes. The discussion hardly serves to diminish the present hiatus between statements about neural function and the psychologist's behaviour statements.

The behaviourist's strategy of denying awareness—at least during working hours and outside the coffee room—has been consistently, and surely rightly, rejected by Eccles for many years. With recent interest in language and cognitive perceptual processes the classical behaviourist position seems not only arid but dishonest in rejecting vital if inscrutable facts about human beings. The question is: Does neurophysiology, or current psychology, have concepts sufficiently rich to include awareness? Eccles feels the limitations of existing concepts, and as a result he is drawn to something close to theology. Other scientists may feel that this merely hides the problems under a heavenly carpet—no better than sucking it up in the behaviourist's vacuum—when what are needed are new insights. It is not at all certain that these will come from analysis of neural function at the synaptic or cellular level. R. L. GREGORY

Was Hitler a Scientist?

The Scientific Origins of National Socialism: Social Darwinism in Ernst Haeckel and the German Monist League. By Daniel Gasman. (History of Science Library.) Pp. xxxii+208. (Macdonald: London; Elsevier: New York, February 1971.) £4.

THIS is a perplexing book about an important subject. Despite my very strong reservations about the approach Dr Gasman has taken here, I cannot recommend that his work be ignored by those who are interested in the interaction of science and politics.

In pursuing his theme of the relationship between the social thought of Haeckel and his followers, on the one hand, and Hitler's seizure of power on the other, Gasman falls into two sorts of fundamental error. First, he tends to oversell his thesis. At one point the reader is told that Haeckel's social Darwinism was "one of the most important formative causes for the rise of the Nazi movement". "Cause", in this instance, is a rather slippery con-

cept, one which begs the question as to how the intellectual tendencies of one era are translated into the political programmes of a later period. Except in one important instance (to be discussed shortly), the author never really faces up to this problem. Instead, he stresses guilt by association: any Monist position later espoused by the Nazis automatically becomes characterized as "bizarre", "sinister" and, presumably, influential.

Second, Gasman fails to establish the uniqueness of Haeckel's approach to the social problems of the late nineteenth century. In fact, as a German university professor in the 1890s, it would have been unusual if he had not been, as he was, a reactionary imperialist both opposed to democratic politics and obsessed with the possibility of national decadence. More importantly, the conjunction of social Darwinism, imperialism and racism associated with Haeckel and his followers was to be found elsewhere, particularly in Edwardian England. When comparisons are made between the histories of Britain and Germany in the thirties, it is not at all obvious how much ideological factors should be stressed in accounts such as Gasman's.

Apart from these difficulties, I still do not understand the relationship between the German Monist League and National Socialism. This organization, founded in 1906, was neither a "scientific" nor a "political" body but rather one devoted to Haeckelian naturalism. Nevertheless, until shortly after the First World War, Monism was often identified with extremely conservative social policies. But after Haeckel's death in 1919, the league swung over to what the author calls "radical liberalism" and maintained this position until the organization was dissolved by the Nazis in 1933. How could this turnabout have occurred? Gasman does not tell us; his account does not include the Weimar period. What are we then to make of his chapters on the social and political assumptions of the Monists? Did they have a genuine change of heart during the Great War, or did the league merely reflect the views of those who just happened to be in power? We just do not know, partly because the author never attempts to discuss the social composition of its membership. Again his purely intellectual approach appears to have failed him.

Yet I am satisfied that Gasman has proved one thing, namely that Hitler himself was directly influenced by Haeckel's romantic vision of "science". Hitler's worship of nature, his hatred of a Christianity which would set man apart from nature and his belief that only "science" (really natural history) could overcome superstition are all

themes derived from the popular writings of Haeckel. The author, as usual, wishes to go further than this, even implying at one point that Haeckel's position on the Jewish question (assimilation) was different only in degree rather than kind from Hitler's (elimination). Here the tendency to overstatement begins to border on the irresponsible.

It is a pity that Dr Gasman has not been content to stay within the terms of such intrinsically interesting evidence. Having seen Hitler from this perspective, I am reminded of the fact that, in our own century, even the most "irrational" of movements will at some point seek "scientific" validation.

P. G. WERSKEY

Primates Not Men

Primate Behavior: Developments in Field and Laboratory Research, Vol. 1. Edited by Leonard A. Rosenblum. Pp. xii+400. (Academic: New York and London, November 1970.) £8.15.

THIS new series brings together reviews and new material on the behaviour of primates (presumably sub-human, though this is not specified) from field and laboratory. In the first chapter of this volume, Rumbaugh reviews data from a variety of situations on the learning skills of primates. Although he emphasizes that at present "we have nothing better than a toe hold" so far as understanding the complexity of primate learning goes, he presents evidence showing not only the extent to which species differ but also the nature of the differences. Emphasizing the behavioural superiority of the great apes over monkeys, he holds that their ability to innovate upon their experiences and to play games implies higher-order ideational processes.

Bernstein presents a much needed review of the diverse and often unsatisfactory literature on primate status hierarchies, accompanied by some new data on groups of several species at the Yerkes Field Station. While the direction of agonistic relationships was stable in nearly all cases, there was little correlation between aggressive, mounting and grooming relationships. The data indicate that a more refined approach to social interactions is necessary before much progress can be made in their understanding.

Data derived from choice experiments on social attachments in rhesus monkeys are reviewed by Sackett. The existence of attachment mechanisms independently of experience is indicated by the preference of infants, reared without access to animals other than age-mates, for female adults of their own species over other categories, and by their age changes in sex preferences. Early social experience,

however, affects later choice of partners, as does also the adequacy of mothering in mother-reared infants, suggesting that the maintenance of attachment depends on the quality of social feedback. Much of this material has not been published previously.

Sorenson's chapter provides a review of many aspects of the anatomy, physiology and behaviour of tree shrews, and includes much new material. Their taxonomic position is honestly recognized as transitional. The literature on behavioural abnormalities in primates is reviewed by Mitchell. A large part of the chapter is concerned with the abnormalities encountered after various conditions of social deprivation at the Wisconsin laboratory, but much other material is included. Finally, the results of 1,250 hours of field observation on *Presbytis johnii* are brought together by Poirier—a valuable contribution to our knowledge of field behaviour and ecology.

If these standards are maintained, this series should do much to bridge the present gap between experimentalist and field worker.

ROBERT A. HINDE

Ecologist on the Farm

Grassland Ecology. By C. R. W. Spedding. Pp. xii+221. (Clarendon: Oxford; Oxford University: London, March 1971.) £2.00.

THIS book is described as "a functional anatomy of grassland ecology for readers who may be specialists in some of the components but relatively new to others". The acceptable thesis is advanced that grassland ecology is a complex ecosystem in which climate, soil, plants and grazing animals are major interacting parts, each of which in turn is composed of interacting sub-components. Most grassland research workers pay lip service to this concept, but for various reasons concentrate their work on component parts in isolation, thereby limiting its relevance to the ecosystem. The author has applied an ecological approach to grassland knowledge and, in effect, has constructed a basic model of the grassland ecosystem.

Seven chapters deal with plant component parts of the model, starting with the individual plant, moving to swards, both cultivated and natural, and ending with the factors affecting the efficiency of primary production. The lack of precision in grassland terminology is decried and it is also stressed that selected processes should not be studied to the exclusion of others equally important. The author notes lack of knowledge on legume senescence and decay in spite of its importance as a source of nitrogen; on how to improve the quantity of nitrogen in circulation in the ecosystem; and on the soil and its processes. The brevity of chapter 6 on natural grassland is sur-

prising, even though there may be no fundamental difference between natural and sown grassland. Most of the world's grasslands are natural plant communities which sustain a large proportion of the domestic grass-eating animals.

Eight chapters are concerned with the fauna of grassland and their interactions with grassland populations. Basic concepts of efficiency in secondary production and the major factors affecting this efficiency are dealt with. Grassland herbage offers a virtually complete diet for the ruminant. Only when much higher performance (of growth, milk yield or reproduction) is required may herbage be inadequate, usually in its content of digestible energy.

The remaining five chapters of the book are devoted to the efficiency of production from grassland of milk, meat, wool and hides and to a brief philosophical discussion of the past and potential contribution of grassland to man. Because of the complexity of model building and the need to use quantitative as well as descriptive language, mathematical models of real or simulated data can be built up with the aid of the computer. A useful appendix has been included to show how this can be done.

Throughout the book, the author seeks to draw distinctions between the simplicity of agricultural efficiency measures and the complexity of ecological assessment. It is also noted that the ecosystem approach need not be so complex as is commonly believed since, for example, non-limiting component parts of the model need not be studied in depth. A plea is made for more understanding of ecological principles in order to understand how they may be more fully utilized by the agricultural systems. (In practice, the farmer has always been an applied ecologist.)

The material in the book is well organized and useful lists of references are given at the end of each chapter: author and subject indexes are provided. Editorial lapses are few, mainly in the contents, but in the text, tables and figures the units of energy, mass/unit area and force used do not always accord with recommended SI unit terminology. Overall, the author's ecological approach in the book is successful and a coherent account of the basic grassland ecosystem has been produced at a moderate price. The book can be recommended to all those interested in the role of ecology in the biological sciences.

JOHN FRAME

Mammals Observed

The Life of Mammals. Vol. 2. By L. Harrison Matthews. Pp. 440+30 plates. (Weidenfeld and Nicolson: London, March 1971.) £4.25.

THIS second volume of Dr Matthews's account of various aspects of mam-

malian life reviews the orders and families of mammals with the exception of the Primates. The fourteen chapters progress in an orthodox manner from monotremes and marsupials to cattle and sheep. Except for some rare bats and rodents about which little is known, all the genera of living mammals obtain a mention. The descriptions are chiefly concerned with the habitats, behaviour, ecology and ethology of various mammalian types. Care has been taken to avoid overlap with the topics covered in volume 1, but this means that nowhere in volume 2 is there a complete discussion of the overall characteristics of a genus and the reader must return to volume 1 for fuller consideration of reproduction, adaptation, migration and behavioural aspects. Anatomical and descriptive material has been deliberately reduced to a minimum, just enough to give an impression of the appearance of each type. Where, however, the anatomical adaptations afford "a very pleasant sight", as Edward Tyson remarked on seeing the construction of a porpoise, there is no hesitation to expand the description.

It is impossible not to share with Dr Matthews his delight in observing living mammals and in collecting information and first hand accounts on their habits. He discusses whether it is true that hedgehogs carry off fruit by impaling it on their spines and comments on their resistance to wasp stings and strikes by adders. We learn how moon rats can be caught in traps baited with bananas and how the pygmy anteater gives a peculiar little sneeze when startled. Many of the curious behavioural manifestations of living mammals are commented upon in a lucid, lively and informative style. The account is, however, by no means limited to a "believe it or not" description of mammalian antics. There is much solid comparative anatomy, embracing skeletal characteristics and general morphology, consideration of functional aspects such as antler shedding, delayed implantation, and constipation in sloths. Dr Matthews also adds much on dentitions but is at a loss to ascribe a function to a narwhal's tusk: perhaps some illustrations of the great variety of tooth form in mammals would have been helpful.

There are some sketches of a few mammals, of a number of heads, and of some morphological features: most readers will wish for more. The thirty plates are all instructive in one way or another, even about the fur coats of big cats, but some indication of size is needed in a few. Many years ago, D'Arcy Thompson wrote a letter to *The Times* regretting that scholarship candidates knew so little about the commoner animals of their world. Here is a book about common and rare mam-

mals which could be read to advantage by both major and minor scholars.

R. J. HARRISON

Natural Nerve Poisons

Neuropoisons: Their Pathophysiological Actions. Vol. 1: Poisons of Animal Origin. Edited by Lance L. Simpson. Pp. xiv+361. (Plenum: New York and London, 1971.) \$22.50.

RESEARCH workers interested in the actions of neurotoxins, or contemplating the use of these substances as tools for the analysis of neuro-physiological function, should find this book useful as an introduction to the subject. By presenting evidence of modes of action it may also help clinicians to devise rational therapy for accidental victims of the poisons. The book is an edited collection of 15 chapters, by 17 contributors, covering the marine poisons tetrodotoxin and saxitoxin, the low molecular weight protein neurotoxins from elapid and crotalid snake venoms and the high molecular weight tetanus and botulinum toxins. Although the emphasis is on the neurotoxins, several chapters also deal with other actions such as the cardiovascular, haemolytic and coagulant effects of the snake venoms and the botulinum haemagglutinin.

As each chapter is written by a different author, it is unavoidable that some unevenness is noticeable, but it has probably been reduced by editing. Editorial control also appears to have avoided a lot of overlapping between chapters, except for some repetitive duplication in chapters 7, 8 and 9. Many of the chapters are well balanced detailed reviews of published (and occasional unpublished) work. A few authors have contributed more personal summaries centred around their own work. I was particularly pleased to find that Yasumi Ogura had contributed a chapter on tetrodotoxin and puffer-fish poisoning. He has made many contributions but most of them are written in Japanese, or are otherwise difficult of access, and his chapter provides a very useful guide to this and to other Japanese work that will be of help to English readers.

The most serious criticism to be made of the book is that many of the references are inaccurate. In one or two chapters these inaccuracies are so many that the only possible explanation is that the manuscript was carelessly prepared. Some of the citations in the text are not listed among the references, or appear under a different date. More serious are the occasional references to an irrelevant publication. This sort of careless error tends to reduce the value of the work for those who wish to use it as an introduction to the field. Most of the chapters are well illustrated,

generally with figures taken from other publications. The line drawings have reproduced well. The half-tone oscillograms are unorthodox with their grey backgrounds but are perfectly satisfactory except for a slight loss of detail when compared with the originals in the *Proceedings of the Royal Society*. Some of the half-tone photographs, however, are unsatisfactory.

In spite of these criticisms the book is a valuable review of a field whose importance to the neurobiologist is increasing rapidly. It would have been pedantic not to have included saxitoxin in this volume because, although it originates in phytoplankton, it is pharmacologically almost identical with tetrodotoxin. One looks forward to the publication of the second volume, dealing with neuropoisons of plant origin, and hopes that the price will not be greater than the already rather high cost of the first volume.

MARTIN H. EVANS

Physics Without Tears

Physics from the Ground Up. By Herman Carr and Richard T. Weidner. Pp. xiv+706. (McGraw-Hill: New York and Maidenhead, April 1971.) £6.95.

IN the past few years, universities and colleges in the United States have produced a remarkable number of introductory physics texts, designed for intelligent students who know little physics from school and who are unlikely to become professional scientists. These books have a number of characteristics in common. They are lavishly produced and rarely run to less than 500 pages, they treat physics from the beginning but at an adult level, they concentrate on the fundamentals at the expense of applications and they rarely use calculus.

This volume fits firmly into this category and must be judged against others of the same genre. On the whole, it is more down to earth, but for that very reason less likely to produce unexpected insights or to illuminate the subject from an unusual angle; it uses two colours to excellent pedagogic and aesthetic effect, its illustrations are outstanding and it has a most useful set of worked problems. In summary, it is a very good and useful example of its kind, and better than many.

There are a number of topics that one can use as touchstones for good textbooks, and on these the present book comes out well. It has a thoughtful treatment of inertial mass, it deals with the hydrogen atom without using either Bohr orbits or standing waves in a circle and it explains Bragg "reflection" clearly and accurately. These are points worth noting.

On the selection of subject matter, I am struck by the fact that it has the datedness of the fashion that has just been superseded. The text is said to fall into five main areas—classical conservation laws, classical interactions, light and waves, the very fast, the very small. The theme is clearly "the physics of elementary particles and all that is needed to lead up to it". But one has grown a little disillusioned with the frontier of science approach to physics textbooks, with the last chapter giving a necessarily confused account of our confused state of knowledge of elementary particles. There is nothing, for instance, on the solid state, liquids or aerodynamics; in other words, there is little or nothing that makes one feel that physics is useful and linked with everyday life.

And yet it is a good book to have around. It is obviously too expensive for English students to buy and it also deals with a pedagogical problem that we do not normally attempt to tackle—that of starting physics at college level. It deserves a place on the shelf of both the sixth form and undergraduate library and it should join the growing band of American textbooks which sooner or later ought to persuade us that to teach physics to the non-physics major is possible and can even be exciting.

L. R. B. ELTON

Stellar Atmospheres Clarified

Stellar Atmospheres. By Dimitri Mihalas. (Series of Books in Astronomy and Astrophysics.) Pp. xiv+463. (Freeman: San Francisco and Reading, February 1971.) £7.50.

THE central problem in the theory of stellar atmospheres is to relate "theoretician's" quantities such as total luminosity, effective temperature, surface gravity and chemical composition to "observer's" quantities such as broad-band and narrow-band magnitudes and the intensities and profiles of spectral features. It is because the latter depend on details of radiative transfer in the outer mass shell of a few $g\text{ cm}^{-2}$ from which radiation escapes to space and to the observer that the small "tail" of a star formed by its atmospheric layers assumes an importance out of all proportion to its mass and is being studied with computers and other means as actively as the theory of stellar evolution itself. This problem of radiative transfer is not by any means the only interesting problem connected with stellar atmospheres, but other questions (such as the origin of chromospheres, coronas and the solar cycle) are outside the scope of the book under review—a reasonable limitation in view of the

vastness that the subject has now reached and in view of the different and generally less well understood character of the physics in the other problems.

Classical studies of stellar atmospheres were compelled by limitations in knowledge and computational facilities to make a number of simplifying assumptions, usually the following: stratification in plane parallel layers, radiative equilibrium (except when this leads to superadiabatic temperature gradients), hydrostatic equilibrium and local thermodynamic equilibrium (LTE). The last assumption, while often a good approximation in practice, is not strictly self-consistent and has been strongly attacked in recent years. A more logical approach is to assume only that, at each depth, the populations of various energy levels are in a steady state. Both LTE and non-LTE (i.e. steady-state) models require computers to obtain accurate solutions for most realistic cases and in this field some of the most important contributions have been made by Professor Mihalas, who has settled a number of old controversies by the sheer quality of his work. His textbook, therefore, awakens (and largely fulfils) the highest expectations.

The book is devoted to the basic mathematics and physics of the following problem: given a plane-parallel atmosphere in hydrostatic equilibrium and with known chemical composition (mainly hydrogen and helium), to predict the temperature structure, level populations and emergent spectrum as a function of the effective temperature both with and without the assumption of LTE. Applications are given mainly for the hotter stars, because their spectra are dominated by the mathematically most tractable atoms, hydrogen and helium.

The treatment is lucid and largely self-contained, starting with radiation quantities, the equation of radiative transfer and an outstandingly good treatment of grey atmospheres and mean absorption coefficients. Microscopic concepts are then introduced: equations of state, ionization and dissociation; and emission, absorption and scattering treated by both classical and quantum-mechanical methods. The introductory section ends with a discussion of equations of statistical equilibrium and the roles of radiative and collisional transitions, and is followed by a highly informative up-to-date critical account of the various methods of constructing model atmospheres in LTE including the effects of convection. The methods and results of non-LTE calculations for the continuum (though only in hot stars) are then described.

The remainder of the book is devoted to spectral lines, starting with a very thorough discussion of the absorption profile and redistribution in frequency.

Line formation in stellar spectra is first discussed on the basis of simplified classical models of coherent scattering and pure absorption and the curve of growth is developed by a treatment identical to that of Unsöld. The book concludes with a short but very clear account of line blanketing effects on the temperature structure of the atmosphere, both with and without the LTE assumption.

The reader interested in the more empirical aspects of stellar spectra, especially for stars with effective temperatures less than or equal to that of the Sun, will have to look elsewhere for details. Within his chosen field, however, the author's deep knowledge and exceptional talent for clear exposition have resulted in a brilliant book which could hardly be improved upon as an up-to-date and impartial introduction to current problems in the 'theory of stellar atmospheres'. For several years to come it is likely to be the textbook in its field and it is one of the very few astronomical books that I would recommend both specialists and graduate students to buy. BERNARD PAGEL

Phases to Look At

Phase Equilibria Spatial Diagrams: Phase Diagrams—Their Interpretation and Anaglyph Representation. By F. Tamas and I. Pal. English translation edited by Miss L. S. Ward. Pp. 234 + 72. (Iliffe: London, January 1971.) £4.

THIS book, translated from the Hungarian, provides a novel approach to the problems of visualization of complicated phase diagrams by the use of three-dimensional figures (anaglyphs). It is aimed at both students and "experts" in chemistry, metallurgy, physics and materials science. Only solid-liquid equilibria are dealt with; there is no attempt to discuss phase diagrams for liquid-vapour or solid-vapour systems.

The principles and basic definitions of the subject are outlined very concisely in the first 11 pages of the book at a level to be found in most general textbooks of physical chemistry. The rest of the book is devoted to the practical applications of these principles to some 80 or so systems. Binary systems occupy 62 pages, ternary systems 112 pages and quaternary systems 20 pages. A novel systematic notation is used throughout. The last 70 or so pages of the book are devoted to the three-dimensional drawings referred to in the main text, and these are printed as superimposed pairs in red and green to be viewed with the red and green spectacles provided (two pairs) with the book. They vary considerably in complexity, and the success of the three-dimensional effect, for the reviewer, also

varied greatly; for some of the more complicated diagrams, I found it easier to close one eye and so view only the two-dimensional representation, but many of the diagrams were very effective indeed in three dimensions. Most people have one eye dominant and so any prospective purchaser would do well to check carefully that this method of obtaining the three-dimensional effect does in fact "work" for him, since these diagrams constitute a major part of the book.

There is a useful index of the 79 chemical systems discussed, but the subject index is extremely brief, occupying less than a page. Both indexes use paragraph reference numbers rather than page numbers, which to my mind makes them more difficult to use, especially since the paragraphs may occupy up to a dozen pages. Few specific references are given, 27 in all, of which only nine are to papers written in English.

The set of examples provided by this book goes well beyond the breadth of knowledge of applications of the phase rule to solid-liquid equilibria that chemistry undergraduates in Britain are likely to need, but the three-dimensional figures should be useful. Those trained chemists not accustomed to visualizing three and more dimensional surfaces from two-dimensional representations of them may find it useful. Materials scientists should also find it useful. The book is well produced, clearly written, the translation is good and it is good value. G. L. PRATT

Protein Analysis

Protein Sequence Determination: a Sourcebook of Methods and Techniques. Edited by Saul B. Needleman. (Molecular Biology, Biochemistry and Biophysics, Vol. 8.) Pp. xix + 345. (Chapman and Hall: London; Springer-Verlag: Berlin and New York, 1970.)

DESPITE the steady progress of primary structure determination, it seems as if the demands of protein scientists for sequence information will only be met by the development of automatic methods and extensive data processing, supplemented, for the time being at least, by a "do-it-yourself" approach. In a field in which previous books have been few but mostly good, the present work sets out to provide the newcomer with guidance, experimental detail and background literature. The editor makes the point that the diversity of techniques available, which may initially appear confusing, actually provides a flexibility of approach adaptable to individual laboratories.

Pride of place must go to the long-

awaited, authoritative and occasionally pungent review by Edman of the step-wise degradation method that bears his name. Procedures refined by the author over a period of 20 years, culminating in the automatic protein sequenator, are described in detail. Edman gives cogent reasons for preferring positive identification of amino-acid PTHs to subtractive procedures, and this opinion is reinforced by recent developments in the separation and identification of these compounds by GLC and mass spectrometry. Nevertheless, the brief treatment of the dansyl-Edman technique in Narita's otherwise comprehensive survey of *N* and *C*-terminal methods hardly reflects its present utility and popularity. The fluoronitropyridine reagents developed by the Padua school might have been referred to in preference to some of the "Other Chemical Methods", and the use of polyamide layers, currently one of the best methods for separating DNS-amino-acids, is not mentioned.

Von Holde gives a useful summary of physical methods for the characterization of proteins, and Eveleigh and Winter write in a practical way about up-to-date methods of amino-acid analysis, with special reference to Technicon instruments. Linenberg's short chapter on amino-acid analysis by gas chromatography has inevitably been rather left behind by this fast-developing field. Kasper contributes a chapter on methods for peptide bond fission and the separation of mixtures of peptides. Cyanogen bromide, dilute and concentrated acids, and the more specific enzymes are adequately dealt with, but there is no mention of subtilisin, thermolysin, elastase nor "Pronase". Peptide mapping is not described despite a cross-reference on p. 207 (indexed as p. 206), and diagonal electrophoresis gets only a brief mention.

The theme of the chapter by Scoffone and Fontana is the specific reactivity of particular amino-acid residues which serves for their determination and also their detection on paper and other media. Quantitative methods for total protein, tryptophan, cystine and cysteine are given in some detail. The description of disulphide bond reduction and alkylation (p. 202) is duplicated by Kasper (p. 152, where ref. (318) should be (218)). This typifies both a certain amount of repetition that could have been reduced by careful cross-referencing, and too great a prevalence of trivial errors. Goldstone and Needleman discuss the reconstruction of the primary sequence from peptide fragments. The application of computers is described, but the pairing of half-cystine residues is not dealt with. Gish contributes a chapter on peptide synthesis which, as far as I can judge, gives a balanced account of the subject. A useful addi-

tion would have been an account of the synthesis of side-chain-substituted derivatives of amino-acids, particularly lysine and cysteine, which are often encountered in sequence work but may not be easily available. There is no contribution dealing with the use of the mass spectrometer for the determination of sequences.

Although many laboratories will want this book primarily for the chapter by Edman, it does as a whole cover a large part of present-day sequence methodology. But only those who take the trouble to thumb through it and familiarize themselves with the contents will be able to make full use of it as a work of reference, and newcomers to the field would be unwise to rely on it exclusively. J. C. FLETCHER

Oxide Compendium

Landolt-Bornstein. Numerical Data and Functional Relationships in Science and Technology. New Series. Editor in Chief: K. H. Hellwege. Group III: Crystal and Solid State Physics. Vol. 4: Magnetic and Other Properties of Oxides and Related Compounds, Part b. By D. Bonnenberg *et al.* Editors: K. H. Hellwege and A. M. Hellwege. Pp. xvi + 666. (Springer-Verlag: Berlin and New York, 1970.) 428 DM; \$117.70.

THIS book, which completes the fourth part of Volume III of these tables, contains information about three classes of compounds—non-iron garnets, spinels, and hexagonal ferrites. It is a composite work by authors from four different countries—Germany, the United States, France and the Netherlands—and no trouble has been spared to make it comprehensive. Results are published in the form of tables and diagrams, and every conceivable measurement of physical properties seems to have been included together with extensive lists of references.

The compounds are characterized by simple atomic arrangements in which extensive substitution is possible, so that an infinite variety of compositions exists. Each section is preceded by a concise but clear introduction in both English and German, and it is obvious that the authors are more concerned with the fundamental importance of the results than with their practical application. One would have thought that results as extensive as these would have been acquired only if there were some important applications, and this is hinted at, for example, in a diagram on p. 278, which shows an area of a ternary oxide system that is important in microwave research. More indications of this sort would have been welcome.

The book is well indexed in terms of the chemical formulae of the compounds included. It would also have been helpful if an index of physical properties had also

been produced; one can imagine a research project that might require a material with a particular property, and it would require a great deal of searching to find the possibilities from the mass of data included.

The book is impeccably produced in accordance with the well known Landolt-Bornstein tradition. The diagrams are clear and informative and the legends, although only in the language of the originators, are sufficiently simple to be readily understood with minimal linguistic ability. The tables are well set out and uncluttered. Altogether, the book should form a standard work of reference for those whose interests lie in the compounds included. H. LIPSON

Mössbauer Collection

Proceedings of the Conference on the Application of the Mössbauer Effect, Tihany, Hungary, 17th/21st June, 1969. Edited by I. Dezsö. Pp. 808. (Akademiai Kiado: Budapest, 1971.) £11.

THIS book is a collection of ninety-two specialist papers presented at the 1969 Tihany Conference on the Mössbauer Effect. Most of the papers are from East European research groups, so that they give a somewhat one-sided view of the current state of research. All of them have been translated into English, the standard of which is usually good. The chief value of the volume is that it brings together, under one cover, reports of the work of research groups that are not always easily obtained in English.

A comprehensive picture of the wide range of applications of the Mössbauer effect is given by the range of topics covered, divided into the following sections: General Problems, Relaxation Effects, Goldanskii-Karyagin Effect, Surface Phenomena, Alloys, Oxides, Frozen Solutions, Biology, Chemistry and Miscellany. Although there are brief review papers at the start of most of the sections, there is unfortunately no general introduction to the Mössbauer effect nor reference to the many excellent introductory texts now available for the non-specialist. The review papers in biology by G. Long and chemistry by C. E. Johnson are particularly clear and well presented.

Among the individual papers, those by A. H. Muir and M. Blander (extra terrestrial materials), M. A. Andreeva and R. N. Kuzmin (narrowing of Mössbauer lines) and V. D. Gorobchenko *et al.* (stabilization of hyperfine structure in corundum by a small external magnetic field) are particularly noteworthy. It is, however, a pity that in general many of the spectra on which detailed discussions are made are of such a relatively poor quality. Often a modest increase in running time would have yielded many more convincing data.

F. W. D. WOODHAMS

CORRESPONDENCE

Academy Expulsion

SIR,—In his report "Academy Squirms a Little in Sudden Spotlight" (*Nature*, 231, 6; 1971), your Washington correspondent concludes: "Nonetheless, the academy's standing among many younger scientists would probably be more enhanced if Lewontin were to be persuaded to remain a member and Shockley expelled". Would he be willing to describe in *Nature* how such an expulsion might be accomplished?

Yours faithfully,

B. A. RASMUSEN

Department of Animal Science,
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of all Indian workers for one reason or the other. Further, Indian workers do not have the privilege of having a 'Xerox' service. Even where it is available, the cost involved is prohibitive. May I therefore request, through your columns, that requests for reprints from developing countries should be given priority by investigators working in affluent circumstances?

Yours faithfully,

SHANTA S. RAO

Institute for Research in Reproduction,
Indian Council of Medical Research,
Jehangir Merwanji Street,
Parel,
Bombay-12

Reprints for India

SIR,—It has been the experience of many Indian research workers that requests for reprints, particularly when made after the journals were received in this country, invariably brought regret cards. The *Current Contents* has helped to overcome this handicap to some extent. But even now we find that requests for reprints draw only negative replies. Many of the foreign journals are not within the reach

Philadelphia (Ph-1) Chromosome

SIR,—Belatedly, I have read the March 19 issue of *Nature*, with the paper by O'Riordan *et al.*¹ describing the identification of the Philadelphia chromosome, and your editorial comment "Still More Light on Human Chromosomes"².

In 1970, Drs Prieto, Forteza, Marco and I had the opportunity to study a woman with chronic myelogenous leuk-

aemia and a marker Philadelphia (Ph-1) chromosome³. Using autoradiography, we demonstrated that the Ph-1 chromosome had originated from a member of the early replicating, G-22 pair, and thus was different from the late replicating^{4,5}, G-21 chromosomes responsible for mongolism when in triplicate. O'Riordan *et al.*¹, using quinacrine fluorescence, have confirmed our findings while ignoring our work. Their results, no doubt, are extremely interesting, but neither the authors nor your editors² would have found them "unexpected" had they taken the trouble to read our paper, "Identification of the Philadelphia (Ph-1) Chromosome", published about a year ago.

Yours faithfully,

J. EGOZCUE

Instituto de Biología Fundamental,
Universidad Autónoma de Barcelona,
Barcelona

¹ O'Riordan, M. L., Robinson, J. A., Buckton, K. E., and Evans, H. J., *Nature*, 230, 167 (1971).

² *Nature*, 230, 145 (1971).

³ Prieto, F., Egozcue, J., Forteza, G., and Marco, F., *Blood*, 35, 23 (1970).

⁴ Yunis, J. J., Hook, E. B., and Mayer, M., *Lancet*, i, 465 (1965).

⁵ Yunis, J. J., Hook, E. B., and Mayer, M., *Amer. J. Hum. Genet.*, 17, 191 (1965).

Announcements

University News

Professor D. V. Lindley, University College London, has been appointed visiting professor of statistics in the Department of Mathematics of the City University.

The following appointments have been made in the University of London: Professor M. Ledingham, to the chair of medicine tenable at London Hospital Medical College; Professor J. K. T. L. Nash, to the chair of civil engineering tenable at King's College; Dr A. S. Truswell, to the chair of nutrition and dietetics tenable at Queen Elizabeth College.

Professor L. R. B. Elton has been appointed to the new chair in science education within the Institute for Educational Technology, University of Surrey, and Professor J. A. Lauwerys has been appointed visiting professor in the Institute.

Miscellaneous

Dr Lionel Cox, Macmillan Bloedel Limited, and Mr V. N. Mackiw, Sherritt Gordon Mines Limited, have been appointed to the National Research Council of Canada.

Dr H. R. L. Streight, DuPont of Canada Limited, has been elected president of the Chemical Institute of Canada. The new president-elect is Professor Pierre Grenier, Laval University.

Mr S. R. Badley, BP Chemicals International Limited, has been appointed chairman of council of the Rubber and Plastics Research Association of Great Britain, in succession to Mr Harry Jackson.

Dr J. B. Armstrong, executive director of the Canadian Heart Foundation, has been elected president of the Biological Council of Canada for 1971-72, and Dr

Michael Shaw, University of British Columbia, has been elected vice-president.

The following elections were made at the anniversary meeting of the Linnean Society: president, Professor A. J. E. Cave; treasurer, F. R. Goodenough; secretaries, Professor R. D. Purchon, J. P. M. Brenan and Dr D. M. Kermack; vice-presidents, F. R. Goodenough, Dr R. W. J. Keay, D. C. McClintock and Dr H. P. Whiting. The Linnean gold medal was awarded to Dr C. R. Metcalfe, formerly keeper of the Jodrell Laboratory, Kew.

Nominations are invited by the Biochemical Society for the awards of the Colworth medal 1971 and the Ciba medal and prize 1971. The Colworth medal, donated by the Unilever Research Laboratory, is awarded annually to a young British biochemist, and the recipient is expected to deliver a lecture at a meeting of the Society and at one of the Unilever research laboratories. The Ciba medal and prize of £50 will be awarded for outstanding research in biochemistry carried

out in Great Britain or Northern Ireland, and is open to candidates of any nationality. The recipient is expected to deliver a lecture at a meeting of the Society. Nominations for both these awards should reach the executive secretary of the Biochemical Society, 7 Warwick Court, London WC1R 5DP, before September 30, 1971.

A new Presidium of the Academy of Sciences of the USSR was elected at the annual general meeting of the Academy (May 25–28, 1971). Academician Mstyslav V. Keldysh was re-elected as president of the Academy. The following academicians were elected as vice-presidents: M. D. Millionshchikov, V. A. Kotelnikov, A. N. Belozerskii, A. P. Vinogradov, P. N. Fedoseev, and M. A. Lavrent'ev. Corresponding Member of the Academy, G. K. Skryabin, was elected to the post of academic secretary.

The remainder of the new Presidium consists of the ex-officio members—the academic secretaries of the branches of the Academy, Academicians N. N. Bogolyubov, L. A. Artsemovich, M. A. Markov, M. A. Styrikovich, B. N. Petrov, A. N. Nesmeyanov, N. M. Zhavoronkov, A. A. Baev, E. M. Kreps, Ya. V. Peive, V. I. Smirnov, L. M. Brekhovskikh, V. M. Khvostov, F. V. Konstantinov, N. P. Fedorenko, M. B. Khrapchevko, the chairman of the Presidium of the Ural Scientific Centre, Academician S. V. Vonsovskii, the first deputy chairman of the Siberian Branch of the Academy, Academician A. A. Trofimuk, and the chairman of the Presidium of the Far Eastern Scientific Centre, A. P. Kapitsa. The elected members of the new Presidium are Academicians A. P. Aleksandrov, V. A. Ambartsumyan, N. G. Basov, P. L. Kapitsa, N. V. Mel'nikov, N. I. Muskhelishvili, B. E. Paton, I. G. Petrovskii, N. A. Pilyugin, P. N. Poselov, A. M. Prokhorov, A. M. Rumyantsev, N. N. Semenov and V. M. Tuchkevich.

ERRATUM. In the article "Some Aspects of the Evolution of Hearing in Verte-

brates" by G. A. Manley (*Nature*, 230, 506; 1971), the following corrections should be made: the formulation on line 8, paragraph 3, p. 508, should read L/Ww:WwXWn; reference 30 in the last line of column 1, p. 508, should read reference 31; reference 30 in line 15 of column 2, p. 508, should read reference 32; the legend to Fig. 6 should read "Correlations between the dimensions of the basilar membrane (membrane value/100) and . . . ; B, bat (*Myotis* sp.)".

ERRATUM. In the article "Cranium of the Late Palaeocene Primate *Plesiadapis tricuspidens*" by Frederick S. Szalay (*Nature*, 230, 324; 1971), the following changes should be made. Paragraph 1 should read: "Although Palaeocene primate crania other than that of *Plesiadapis tricuspidens* are known (R. W. Wilson and I are now describing a crushed skull of *Palaechthon alticus* found by R. W. W.), the slightly crushed and damaged skull of the French primate (CR 125), expertly described by Russell^{1,2}, is still the only near complete cranium of a Palaeocene primate. In addition to Russell's excellent descriptions and studies there have been three reconstructions of this unique specimen, one in 1960 and one in 1964 by Simons^{3,4} and one by D. E. Russell². Since Simons's 1964 figure is an improvement, in most respects, over his 1960 reconstruction, my remarks will be directed to his 1964 synthesis". Paragraph 5 should read: "The earlier reconstruction of the anterior region of the skull and of the occlusal relationships may have been faulty because a mandible was fitted with the cranium which had a diastema of distinctly different proportions between the enlarged incisors and premolars from that of the skull, CR 125 . . .".

ERRATUM. In the article "*Ramapithecus wickeri* Mandible from Fort Ternan, Kenya" by Peter Andrews (*Nature*, 231, 192; 1971), Fig. 2 is not natural size but 1.6 × natural size. Line 21 of the second column on p. 193 should read "which is greater the greater the vertical distance between . . .".

British Diary

Tuesday, June 15

A Minoan Country-House and Settlement at Pargos, Myrtos, Crete (5.45 p.m.) Mr G. Cadogan, University of London, at the Institute of Classical Studies, 31–34 Gordon Square, London WC1.

Magnets, Pencils and Paperclips—Discovering New Things About Electromagnetism (5.30 p.m.) Professor E. R. Laithwaite, Royal Institution, at 21 Albemarle Street, London W1. (Lecture for Fourth Form Pupils from Schools in London and the Home Counties. To be repeated on June 16, 22 and 23.)

The Effect of Surgery and Alcohol on the Ability to Drive a Car (5.15 p.m.) Mr J. Colin and Mr C. Wastell, University of London, at Westminster Medical School, 17 Horseferry Road, London SW1.

Wednesday, June 16

Enteropathogenic *E. coli* (2 p.m.) Dr B. Rowe, University of London, at the Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12.

Thursday, June 17

Annual General Meeting (7.30 p.m.) Royal Society of Tropical Medicine and Hygiene, at Manson House, 26 Portland Place, London W1. **Bugs, Brazil and British Honduras** (8 p.m.) Professor D. S. Bertram.

Friday, June 18

Regional Hypothermia in Conservative Renal Surgery (11 a.m.) Mr J. E. A. Wickham, University of London, at the Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12.

Monday, June 21

Management Techniques for New Managers (vacation school, five days) Institution of Electrical Engineers, at the University of Manchester.

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